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ANNALS of SURGERY

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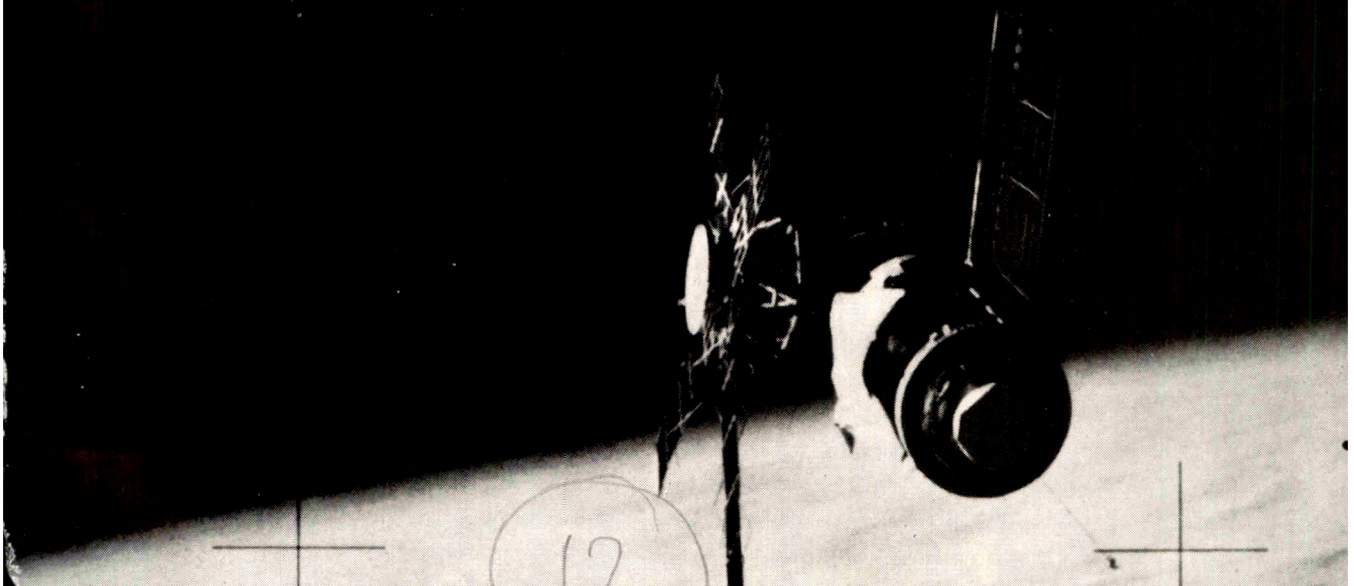
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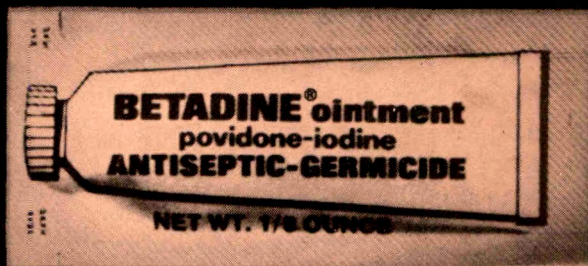
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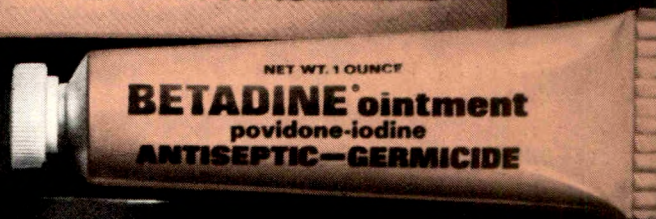
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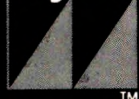
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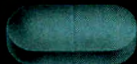
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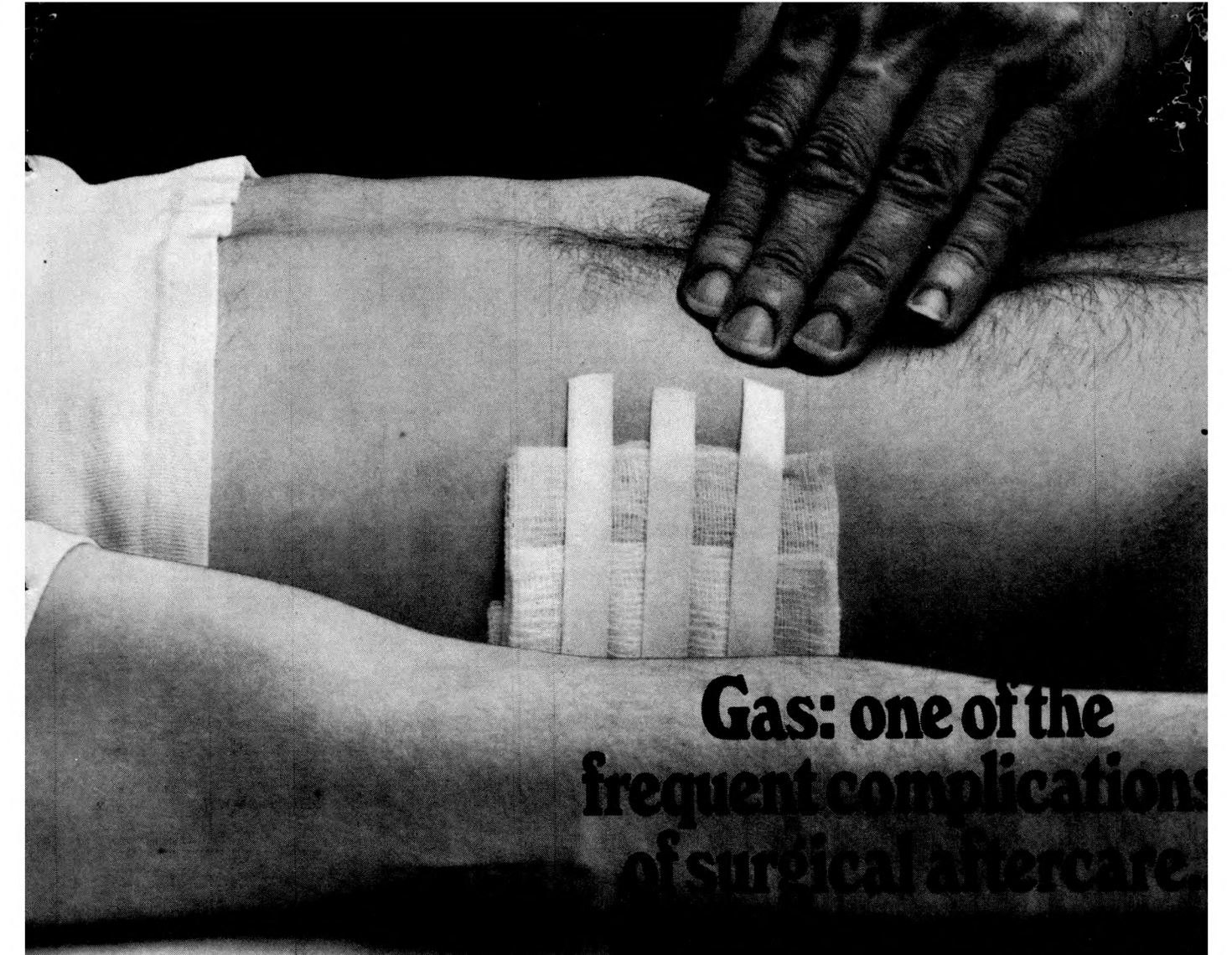


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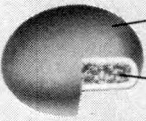
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1. Gibstein, A., et al.: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol.* 38:386, Sept. 1971
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Med/Surg PARKE-DAVIS

Book Reviews

Abdominal Operations. Rodney Maingot and British and American Contributors. Sixth Edition, two volumes, 2240 pages, \$82.50. New York, Appleton-Century-Crofts, 1974.

FOR ONE who recalls the appearance of the first edition of this work in 1940, the publication of the extensively revised sixth edition cannot but arouse a feeling of respect for its durability along with a twinge of nostalgia. Its two volumes reflect the great progress which has taken place in abdominal surgery since 1940. The participation of 43 Americans among the 97 eminent contributors make this a truly international effort. Its principle aim is to present the technical steps of abdominal operations, yet such matters as pre and postoperative care, the selection and effects of operations are not neglected.

A certain amount of folklore persists from previous editions, but there is much that is new. There are excellent accounts of fiberoptic endoscopy; its value in determining the source of upper GI bleeding, and its replacement of transcolonic removal of polyps. Angiography is discussed mainly in reference to tumor diagnosis with only passing reference to its value in trauma and localization of hemorrhage. The efficacy of lymphangiography in staging of Hodgkin's disease is noted. There is no mention of surgical staging, although attention is directed to the extended indications for splenectomy.

The chapters dealing with the identification and management of the sequelae of gastric operations are most instructive. One may also read with interest and profit on such diverse topics as current theories of the pathogenesis of cholelithiasis, new methods of dealing with retained common duct stones, liver transplantation, Nissen fundal plication for symptomatic esophageal hiatus hernia, distal splenorenal shunt for portal hypertension, the "blow hole" operation for toxic megacolon, the "no touch" isolation technique for resection of colonic carcinoma, electrocoagulation of rectal carcinoma, Burkitt's theories of the relation of diet to diseases of the colon, the role of chemotherapy and immunotherapy, in addition to the comprehensive accounts of standard operative procedures.

It is regrettable that some of the 1727 illustrations in which the editor takes such pride have suffered in reproduction and others are difficult to interpret because of inadequate labeling. Moreover, there is an annoying tendency to repetitiousness in the text. In general, however, Mr. Maingot is to be complimented on this readable and informative work which should serve as a valuable reference to surgical residents and practicing surgeons alike.

CARL P. SCHLICKE, M.D.

Nontoxic Goiter. Concept and Controversy, JOEL I. HAMBURGER, M.D., Charles C Thomas Publisher, 1973.

THE PURPOSE of this 200 page monograph is to "assist the physician to determine appropriate management for

thyroid patients in the most expeditious and least expensive fashion." It consists of chapters on thyroid scanning, simple goiter, thyroiditis, clinical evaluation of thyroid nodules for malignant potential and six chapters on thyroid cancer including pathology, surgery, radiation therapy, protocol for management, experience and illustrative cases. This text represents the distillation of a vast amount of clinical experience and a thorough knowledge of the literature. The views are lucidly presented, rational and offer an approach that would be endorsed by the majority of workers in this field today. The initial chapter on thyroid scanning is extremely well done. The discussions on thyroid cancer emphasize the variations in biologic potential of this disease. Particularly instructive is the chapter on the use of radioactive iodine in the management of thyroid cancer. However, the number of patients found suitable for therapy with radioiodine seemed unusually high.

This reviewer would disagree with some of the views; namely, the use of ^{131}I to procure regression of a nodular goiter, the limited role of needle biopsy and the limited role of suppressive therapy in nodular goiter. However, the author was not adamant in his position and presents a rational approach.

Overall, this should be a valuable text for individuals interested in thyroid disease as well as for those who have reason to evaluate only an occasional patient. Reading time is four hours.

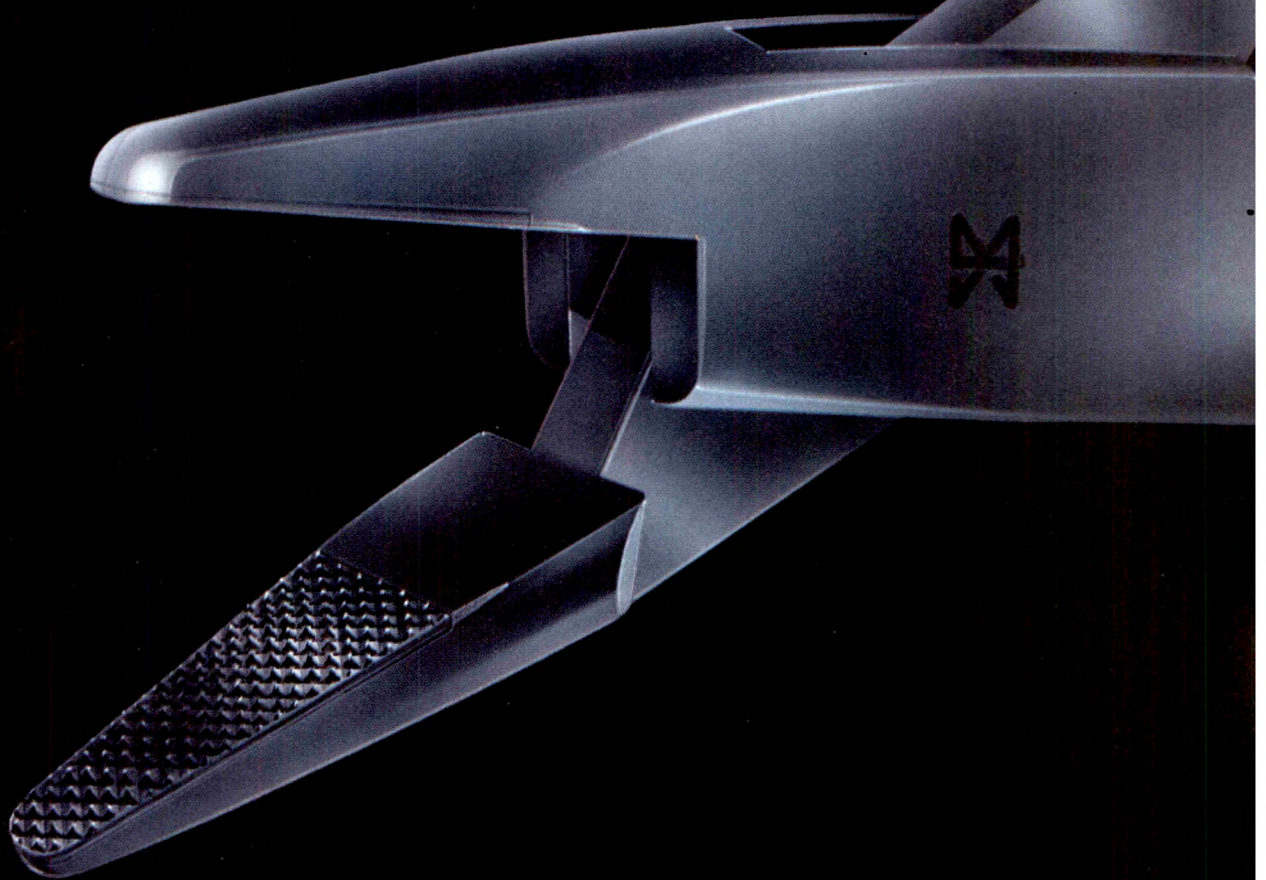
COLIN G. THOMAS, JR., M.D.

The Pancreas. LARRY C. CAREY, St. Louis, C. V. Mosby Company; 1973.

THE EDITOR has assembled a distinguished list of contributors who have brought together under single cover an extensive amount of information. The work is organized into five parts which include the Normal Pancreas, the Abnormal Pancreas and Inflammatory Diseases, Neoplastic Disease and special considerations which include Trauma Transplantation, Diabetes, Anomalies and Lesions of Infancy and Childhood. There are twenty chapters comprising the five parts. The book is well printed and the type is easy to read. The index appears to be complete. Each of the twenty chapters within the text is supported by bibliographies which vary in comprehensiveness. In general, the figures are sharp and clear except for Figure 10-6 which is difficult to interpret.

Overall, this will be a welcome edition to the libraries of those who have an interest in pancreatic problems. Unfortunately it will not be as valuable to non-surgical readers since physiological information presented in Part 1 is relatively incomplete. The chapter on physiology has neglected the important contributions of Webster, which have provided great insights into the control of enzyme formation and secretion. The section on inhibitors is excep-

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Med/Surg **PARKE-DAVIS**

Book Reviews

Finally good although the chapter suffers from a lack of illustrations which will inhibit some readers in obtaining a complete understanding of the text.

The chapter on medical management of acute pancreatitis emphasizes the use of central venous pressure monitoring, a technique which is somewhat outdated at this time. Most modern intensive care units employ flow directed catheters to sample left atrial pressure and to obtain cardiac outputs in patients with overwhelming illness due to acute hemorrhagic pancreatitis.

The chapter on cancer of the pancreas is complete, well illustrated and presents data derived from surgical experiences as well as the more recent anecdotal accounts of chemotherapy for this widespread disease. The chapter on surgery for acute pancreatitis has neglected to stress the problem of suppuration in the retroperitoneal area and lesser sac. Overall however, it covers the pros and cons of this therapeutic approach in an excellent manner.

The chapters on chronic pancreatitis and the 95% pancreatectomy are particularly well illustrated (with the one exception noted above) and lucid in their presentations.

This reader must commend the editor for including a chapter on hormone assay techniques which should prove to be a useful reference source for clinicians without experience in this field in enabling them to understand the limitations in interpretation of these tests. The chapter on radiological techniques is very well illustrated and quite complete.

Surgeons will welcome this text in their libraries since the surgical aspects of pancreatic disease are very well covered indeed. I doubt, however, that many surgeons will be willing to accept the new description that the "pancreas like a river should be described from above down" indicating that the right side will now become the distal pancreas. For many years "distal pancreatectomy" has described removal of that portion of the pancreas which exists in the left side of the abdomen. Readers who may have an interest in the intensive and non-operative therapy of patients who are critically ill with acute pancreatitis will find little help and students seeking to further their knowledge concerning pancreatic physiology with particular reference to enzyme synthesis and secretion will be disappointed.

Atlas of Vascular Surgery, Hershey and Calman, St. Louis, C. V. Mosby Company, 1973.

THE *Atlas of Vascular Surgery* by Hershey and Calman, first published in 1963, has been recently updated in its Third Edition. This volume is considerably expanded from its predecessors and includes sections on such topics as the introduction of the Mobin Udon umbrella into the vena cava and the use of the Spark's mandril in peripheral arterial reconstruction. It covers essentially all topics that are commonly considered under the term "peripheral vascular sur-

gery" and omits cardiac and thoracic aortic problems. The volume is well organized and planned. The illustrations are numerous and for the most part, clear.

An experienced vascular surgeon might well take issue with the details in many of the techniques described in this volume but the methods and techniques given are those that have been found to work in the author's hands and, as such, are satisfactory. In a field where improvisation is often needed, stepwise numbered instructions may seem overly didactic but can be helpful to one embarking on this field. It is for such that this book is primarily written and they will find this a very useful volume.

BROOKE ROBERTS, M.D.
Ravdin Institute
3400 Spruce Street
Philadelphia, Pa.

Plastic and Reconstructive Surgery of the Genital Area.

Charles E. Horton, M.D., editor. Boston, Little, Brown, and Company, 1973, \$42.50.

A VERY COMPLETE text on reconstructive surgery of the external genitalia of both sexes gives broad coverage from the historical background, developmental normals and anomalies, psychologic aberrations of intersex and transsexual problems, losses and dysfunctions from trauma and infections, neoplasms, erectile disorders, and coverage problems, with a miscellany of several unique cases. The many authors for the most part are experienced surgeons who write with authority, but the multiple operations offered some problems, especially the reconstructive procedures for hypospadias (21 chapters, 22 authors, 5 by same set of authors), tend to confuse the reader because a definitive discussion of the advantages and disadvantages of one technique over another is not sufficiently presented by about one half the authors.

The evaluation and management of intersexual and transsexual problems are ably discussed, although the early wave of optimism for surgical transformation has not been as enthusiastically advocated as more time has elapsed. The chapters on trauma are valuable with good examples cited. Discussions of surgical treatment of priapism, impotence, and phallus reconstruction tell little of the efficacy of results.

In general, this is a very good text, bringing out the salient points of genital reconstruction. It is very good on congenital problems and especially hypospadias. It is of value to plastic surgeons, urologists, gynecologists and others involved. Although the bibliography of some chapters is skimpy, the chronology of subject matter and complete index and good photographs and drawings make this a useful book.

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Med/Surg **PARKE-DAVIS**

Portal Hypertension as Seen Today by 17 Authorities, vol. XIV, 1st. ed., CHARLES G. CHILD III, M.D., Philadelphia, W. B. Saunders Co., 283 pages, \$13.50.

TEN YEARS have passed since Volume I in the series, *Major Problems in Clinical Surgery*, addressed the liver and portal hypertension. At that time an aura of optimism emanated from the pages to the extent that prophylactic decompression of portal hypertension was considered as an important pathway to be trod toward the goal of a reduction in morbidity and mortality for the cirrhotic patient. In that same volume the discussion of the effects of liver lymph flow and its restriction by thoracic duct size on portal hemodynamics was presented.

Volume XIV also projects an aura of hope for the future, but this is modulated in more temperate terms in view of the experiences which have evolved over this time period. There is emphasis in the chapters by Warren and LeMaigre on the role of hepatic perfusion in the long term morbidity of portasystemic shunt therapy. These papers identify innovative approaches to shunt therapy which seek to preserve perfusion to the liver.

The vast experience of Dr. Voorhees from the College of Physicians and Surgeons has taught us that the incidence of portasystemic encephalopathy following successful shunting may approach 60% in the good risk patients. He has stressed the well documented morbidity which precludes the return to a full and productive life following shunt therapy. The role of prophylactic shunts has been summarized in a very scholarly manner by Dr. Chalmers and he points out the possibility that the final word on this issue may not yet be at hand.

Another new thought which was unknown ten years previously has been exposed by Drs. Mikkelsen and Kern in their description of the influence of acute hyaline necrosis on survival after portacaval shunt. The strikingly deleterious effects of the presence of acute hyaline necrosis is something that must caution all who are active in this field, to search for the histological evidence of this disorder.

Many other fine chapters are included in the table of contents, these provide information by Drs. G. W. Smith, W. C. Maddrey and G. D. Zuidema, Professor Philip Sandblom and Dr. J. G. Turcotte from the University of Michigan where an extensive series of patients with portacaval shunts has been studied. The extensive experiences of Dr. Linton with his splenorenal shunts is well documented and the advances that have been achieved in the therapy of extra hepatic portal hypertension have been summarized by Dr. H. W. Clatworthy, Jr. The summary chapter by Dr. McDermott on the dilemma of shunt surgery is particularly sharp in its definition of the problems and hopes for the future.

In summary, this is an excellent little volume for those interested in the field and who have occasion to treat patients with portal hypertension. Yet, it goes beyond that; I think that the publication of these papers in one volume summarizes the state of the art from its inception to the present time and will form a useful basis from which to judge future accomplishments.

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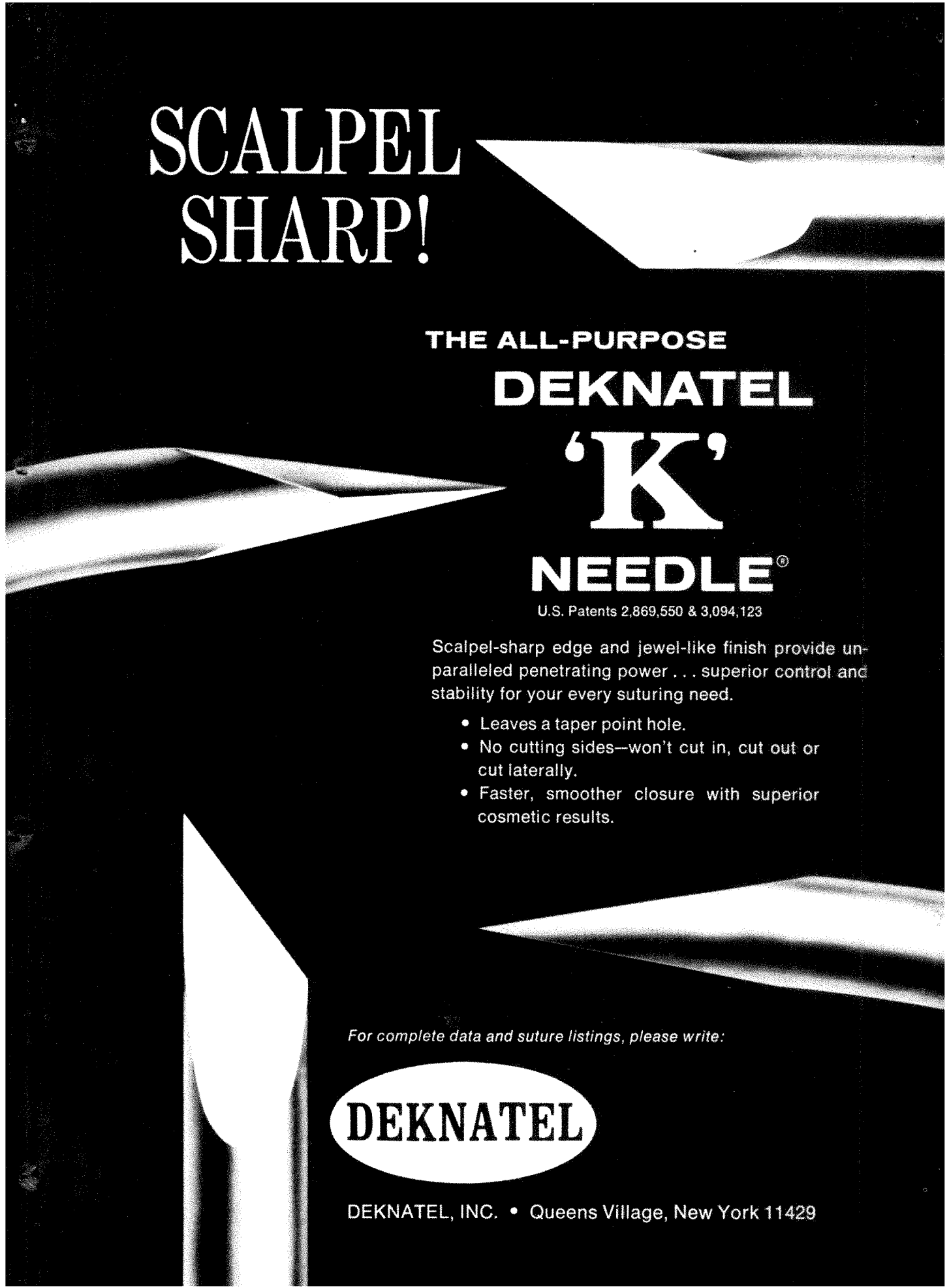
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The Role of Inflammation in Bronchial Stump Healing

RICHARD N. SCOTT, M.D., ROBERT P. FARACI, M.D., DAWN G. GOODMAN, V.M.D.,
THOMAS C. MILITANO, M.D., GLENN W. GEELHOED, M.D., PAUL B. CHRETIEN, M.D.

The roles of inflammatory response and closure technique in the development of bronchopleural fistula were evaluated. Canine bronchial stumps closed with 3-0 silk and studied 14 days later were characterized by a dense inflammatory infiltrate. Stumps closed with 3-0 chromic catgut suture showed a moderate inflammatory response with disintegration of suture material. However, stumps closed with the automatic stapling device (TA-30) showed the best healing and a minimal degree of inflammation. These findings correlated well with leakage pressures. The average leakage pressure for the silk closed stumps was $139.44 \text{ mm Hg} \pm 78.9 \text{ SD}$. This was significantly lower ($P < 0.02$) than the average leakage pressure for staple closed stumps ($251.25 \text{ mm Hg} \pm 82.9 \text{ SD}$). It is concluded that the minimal amount of inflammation following staple closure will be associated with improved bronchial stump healing and a lower incidence of bronchopleural fistula.

BRONCHOPLEURAL FISTULA remains a dreaded complication following pulmonary resections. Because of the high morbidity and mortality associated with this complication, thoracic surgeons have devised numerous technical approaches designed to improve bronchial stump healing.^{2,4,7,26,28,30} These approaches have included alterations in the technique of bronchial stump closure, the use of a variety of sutures and the addition of autologous tissue flaps and synthetic adhesives to the routine operative procedure.^{2,7,16,31} However, despite

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Institutes of Health, Bethesda, Maryland*

these efforts, the incidence of bronchopleural fistula following pneumonectomy varies from 2.7 to 6.7%.^{18,19}

Experimental and clinical studies have emphasized the importance of technical errors in the development of bronchopleural fistula. Infection, devascularization of the bronchial stump, the formation of too long a stump and the failure to cover the freshly sutured stump with surrounding pleura have been cited as common errors.^{18,28,30} However, little attention has been directed toward the inflammatory response between suture and bronchus as compared to studies of the response between suture and other tissues.^{6,10,21}

The purpose of this report is to evaluate the role that this inflammatory response contributes to the strength of bronchial stump closure.

Materials and Methods

Thirty-four adult mongrel dogs weighing 20-25 kg were divided into 2 groups of 17 animals, anesthetized with intravenous sodium barbituate (sodium thiamylal), and intubated. Respiration was maintained by means of an intermittent insufflating apparatus. Left thoracotomy was performed through the fifth intercostal space, and

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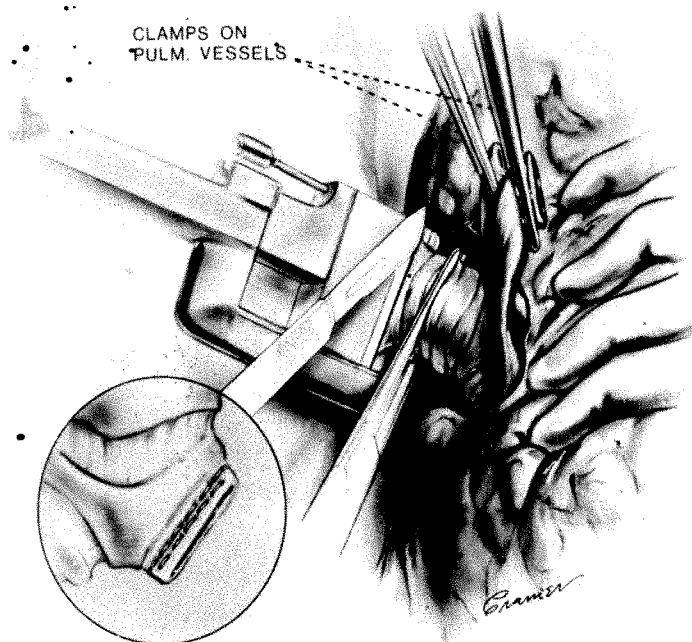


FIG. 1 Application of the automatic stapling device for transection of the left main stem bronchus. Insert shows position of staples in bronchial stump.

the left pulmonary artery, pulmonary veins and bronchial vessels were successively ligated. Trauma to the bronchus and its blood supply was avoided. The bronchus was then transected 1.5 cm distal to the carina.

Group I

In this group, 5 bronchial stumps were closed with interrupted 3-0 silk sutures and 5 with interrupted 3-0 chromic catgut sutures using the modified open technique of Sweet.²⁹ An additional 7 bronchial stumps were closed with stainless steel staples using an automatic stapling device* (Fig. 1) as described by Ravitch.^{23,24} No attempt was made to cover the stumps with additional intrathoracic tissue. At the end of 14 days, all dogs were sacrificed and the stumps excised for histological evaluation of inflammatory response and bacterial cultures.

Group II

In the second group, 9 bronchial stumps were closed with interrupted 3-0 silk sutures and 8 stumps were closed with the automatic stapling device using the techniques mentioned in Group I. Fourteen days following pneumonectomy, all animals were sacrificed, an endotracheal tube was inserted and the left thoracic cavity opened through the previous incision. After the position of the endotracheal tube was verified at the level of the carina, the right bronchus was dissected free and completely occluded. The endotracheal tube was connected

to a cylinder of compressed air with an intervening mercury manometer to measure endotracheal pressure. The left chest was filled with sterile saline and the endotracheal pressure increased until an air leak at the bronchial stump was observed. This pressure was designated as the leakage pressure. The stumps were then removed for histological evaluation and bacterial cultures.

Results

Group I

All bronchial stump closures were grossly similar at 14 days regardless of the type of closure used. All had retracted into the mediastinum and were covered by a thin layer of mediastinal pleura. However, marked histologic differences were noted in the reactions to the three types of closures.

The silk sutures were surrounded by a marked zone of inflammation composed of a mixed inflammatory cell infiltrate. Lymphocytes were the predominant cell type superimposed on a framework of immature and mature fibroblasts. Intermixed with these cells were mac-

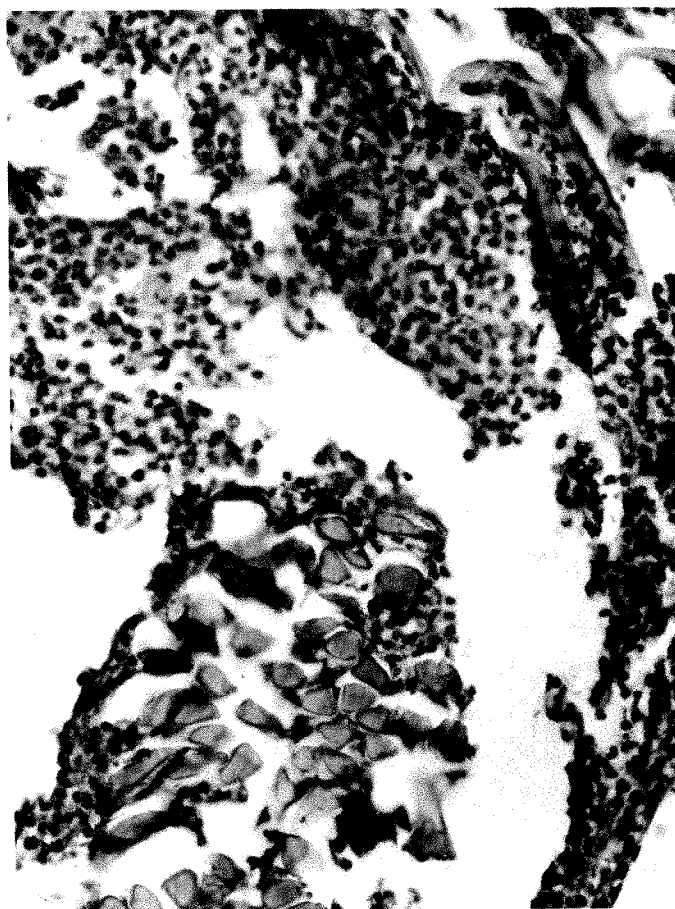


FIG. 2. Silk suture surrounded and infiltrated by a predominantly polymorphonuclear cell infiltrate. (H&E $\times 350$).

*United States Surgical Corporation, 845 Third Avenue, New York, New York 10022.

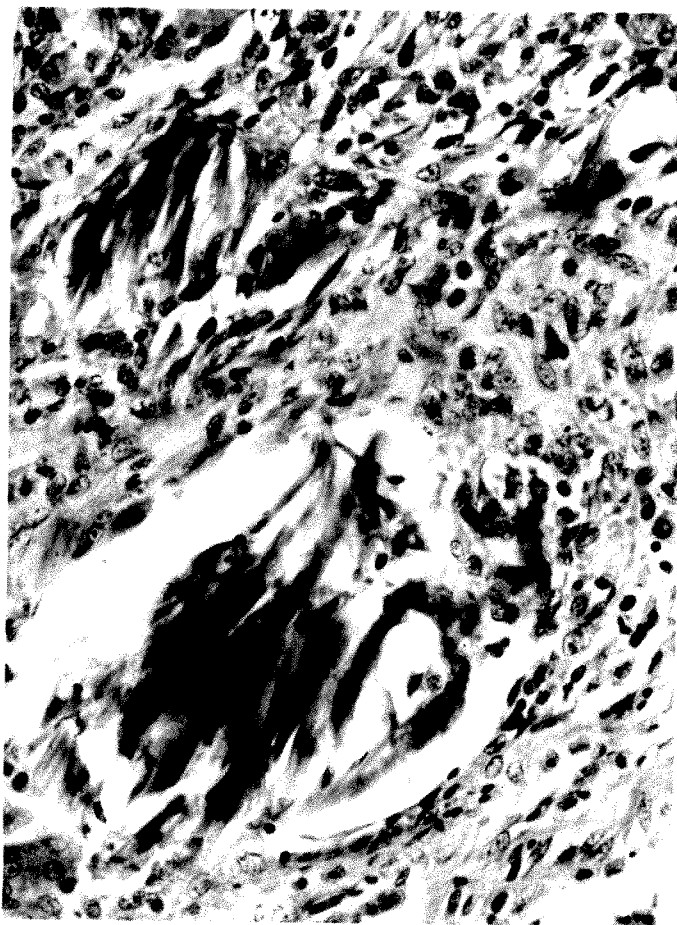


FIG. 3. Fragmented chromic gut suture surrounded primarily by macrophages, lymphocytes and plasma cells with occasional foreign body giant cells. (H&E $\times 375$).

rophages, plasma cells, giant cells, and polymorphonuclear leukocytes (polys), the last two frequently infiltrated between the filaments to surround the individual silk fibers (Fig. 2).

As compared with silk closure, stumps closed with chromic catgut showed less inflammation. The suture material was in various stages of fragmentation and was surrounded partially or completely by foreign body giant cells. The zone of inflammation was extremely variable in diameter and character. Inflammatory cells were predominantly macrophages and foreign body giant cells except with marked fragmentation of the suture material, when polys predominated. Fibroplasia was prominent.

The bronchial stumps closed with the automatic stapling device employing stainless steel staples showed the best healing. A zone of fibroblasts and macrophages 10-15 cells thick surrounding the wire suture was the only evidence of inflammation (Fig. 4).

Cultures of the above three types of bronchial stump closures presented a mixed flora with no specific organism prevalent in any single closure. The organisms included *Staphylococcus epidermidis* and *aureus*,

nonhemolytic *Streptococcus* species, *Proteus* species and *Pseudomonas aeruginosa*.

Group II

This group was studied to determine if the inflammatory response correlated with the strength of closure and was conducted using only silk closures (greatest inflammation) and staple closures (least inflammation). The histological studies and culture results were identical to those of Group I.

The average pressure necessary to cause an air leak in the 8 bronchial stumps closed with staples was $251.25 \text{ mm Hg} \pm 82.9 \text{ SD}$. By contrast, the average pressure necessary to cause an air leak in the 9 bronchial stumps closed with silk was $139.44 \text{ mm Hg} \pm 78.9 \text{ SD}$. The silk closed stumps were significantly weaker ($P < 0.02$) than those closed with staples (Fig. 5).

Discussion

Bronchopleural fistula has plagued thoracic surgeons since 1933 when the first successful pneumonectomy, by Graham, was complicated by this problem.¹⁴ Early at-

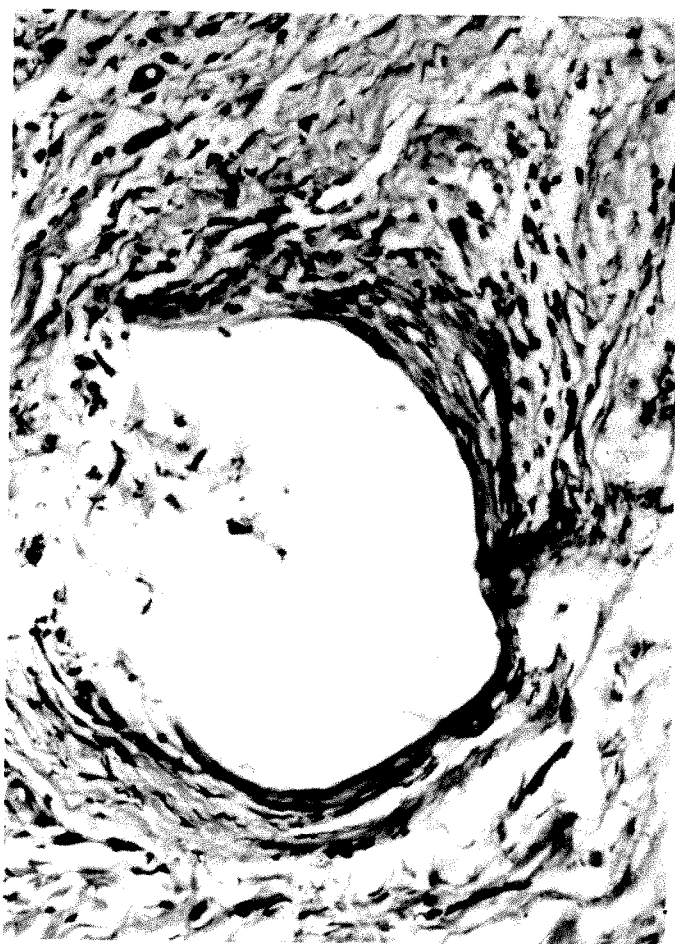


FIG. 4. Site of wire suture surrounded by a thin layer of flattened macrophages and fibroblasts. (H&E $\times 275$).

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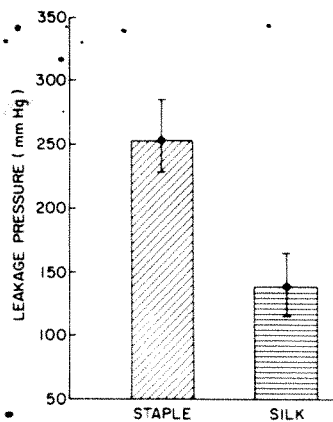


FIG. 5. A comparison of leakage pressures of silk and staple closed bronchial stumps at 14 days.

tempts at preventing bronchopleural fistula included the work of Quinby and Morse in 1911 who emphasized the importance of peribronchial tissue in stump closure.²² Huer and Dunn in 1920 indicated that the type of suture material used in bronchial stump closure did not influence the incidence of bronchopleural fistula.¹⁷ These observations were supported by Rienhoff in 1942 and expanded to indicate that the most important factors in bronchial stump healing are use of a minimal number of sutures for stump closure and coverage of the stump with pleura.²⁵

However, additional factors may be as important in bronchial stump healing. One of these factors, bronchial inflammatory response associated with a type of suture material, requires reevaluation. Recent studies suggest that bronchial stumps closed with non-reactive suture material may reduce the incidence of bronchopleural fistula.^{26,27} One of these non-reactive suture materials, the stainless steel staple introduced by Russian surgeons in 1957, has produced promising results.^{1,3,13,15,20,27} American experience with this instrument (UKL-40) has been extensively reported by Ravitch and Dart.^{9,24} Ravitch reports no bronchopleural fistula in 25 pneumonectomies.²⁴ Dart's experience of 8 fistulae (7%) in 117 pneumonectomies was less encouraging.⁹ However, this variability in incidence of bronchopleural fistula with the Russian stapler may be due to technical problems such as improper manual loading of the individual staples allowing malposition, defective staples or premature loss of staples. An improved American stapler eliminates these sources of error through the use of a prepackaged kit which assures proper alignment of two staggered rows of "B"-shaped staples of uniform length. Using the American stapler, Dart has reported no fistula in 86 pulmonary resections that included 13 pneumonectomies.⁹

Our experimental data suggest that the American stapler (TA-30 Model) may be the most effective method of bronchial stump closure currently available. The minimal inflammatory response at 14 days in those stumps

closed with the stapler was in marked contrast to the dense inflammatory infiltrate present in the silk closures. The degree of inflammatory response correlated well with the strength of closure. The superiority of the staple closure in our experiments may result from the absence of bronchial stump inflammation associated with the stainless steel staples, or increased strength of closure caused by the interlocking rows of staples. Goffi and Goncalves data suggests the latter possibility may be of importance.¹² They demonstrated that canine bronchial stumps closed with either 3-0 cotton sutures or stainless steel wire sutures showed no difference in leakage pressures 7 days following pneumonectomy. Unfortunately, this series did not include bronchial stumps closed with the stapler.

It is difficult to compare the incidence of bronchopleural fistula following stapled and sutured bronchial closures since fistula rates vary with the primary disease and the type of resection done. However, the reported incidence of bronchopleural fistula following sutured stump closure (2.7% to 6.7%) remains unacceptable when the overall mortality for patients developing this complication is an alarming 23.1%.^{18,19} From our studies, we concluded that the relative lack of inflammation following staple closure will be associated with improved bronchial stump healing and a lower incidence of bronchopleural fistula. Inflammation correlates closely with bronchial stump closure and this must be considered by surgeons in their selection of suture material.

Acknowledgments

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The Diagnosis of Jaundice by the Minilaparotomy Open Transhepatic Cholangiogram

H. DAVID STEIN, M.D.

The precise diagnosis of the etiology of jaundice is of considerable value to the clinician in caring for the icteric patient. A series of twenty-three patients who underwent minilaparotomy (open transhepatic cholangiogram) is presented. This procedure allows for inspection, biopsy, cholangiography and omental venography under direct visualization and at minimal risk to the patient. In this series the cause of jaundice was successfully determined in 96% of the cases. Cholangiography was used to visualize the ducts in 20 patients and in 2 others, the diagnosis was made by inspection and liver biopsy. The literature on alternative diagnostic methods is reviewed and compared to other procedures the minilaparotomy has relatively few contraindications and many advantages. It is a useful and safe technique in the face of abnormal clotting factors, obstructive jaundice, ascites or hepatitis. By using the multiple diagnostic modalities available in a minilaparotomy, the rate of successful diagnosis equals or exceeds that of the other procedures. It is therefore recommended that this approach be considered as a diagnostic tool in the evaluation of jaundice.

THE ACCURATE DIAGNOSIS of the etiology of jaundice is of key importance in determining the therapy of the icteric patient. Even after the history, physical examination, laboratory tests and non-invasive radiological studies are completed, the diagnosis is frequently unclear or in error.³

Several procedures have been developed to elucidate the etiology of jaundice. These include: 1) percutaneous transhepatic cholangiography (PTHC); 2) transjugular percutaneous cholangiography (TPC); 3) laparoscopy with transhepatic cholecystocholangiography (LTHC); 4) endoscopic retrograde cholangiography (ERC); and 5) open transhepatic cholangiography (Minilaparotomy) (OTHC).

The multiplicity of procedures attests to the specific problems and limitations encountered with each of them. The following is a series of investigations of obstructive jaundice in 23 consecutive patients using the open transhepatic cholangiogram through the "Minilaparotomy" as described by Strack *et al.*²⁸ The results are presented and the relative merits of the procedures are discussed.

From the Department of Surgery,
Lincoln Hospital, and
The Albert Einstein College of
Medicine, Bronx, New York

Materials and Methods

Twenty-three patients at the Bronx Municipal Hospital Center and Lincoln Hospital were referred to the author for evaluation of jaundice.

The patients were referred if routine diagnostic procedures failed to reveal the cause of jaundice. Five of the patients had ascites and four had elevated prothrombin times (17/11, 18/12, 19/11, 23/10). All patients underwent minilaparotomies performed by the author. The only contraindication to the procedure was known allergy to contrast material. Inability to tolerate general anesthesia was not an obstacle for inclusion in the study. This series does not include any patients who underwent minilaparotomy for evaluation of portal hypertension.

According to the method of Strack *et al.*,²⁸ the liver was visualized through a 4cm subxiphoid incision using local anesthesia. The catheter was inserted into the liver and injection of contrast material made under fluoroscopic control until the contrast was observed to flow into a bile duct. Cholangiograms were attempted in all cases. Since the liver was punctured under direct vision and was always sutured, multiple punctures could be made without fear of bile leakage or hemorrhage. Liver biopsy was carried out with a Vim-Silverman or Menghini needle when indicated. Omental vein portography was performed when a patient was shown to have carcinoma and a Whipple's procedure was being considered. When indicated, cultures of bile and ascitic fluid and cytology were obtained.

Results

OTHC via minilaparotomy resulted in successful diagnosis in 21 of the 23 patients (Table 1). The diagnosis was not made in patient No. 16 in whom cholangiogram was unsuccessful and liver biopsy was interpreted as compatible with extra-hepatic obstruction. At surgery the extrahepatic biliary tree appeared normal. There was normal bile in the gallbladder and a cholecysto-

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TABLE 1. Patients Undergoing Open Transhepatic Cholangiogram (Minilaparotomy)

Case	Clinical Diagnosis Prior to OTHC	Observation	Cholangiogram	Pathology	Diagnosis From Minilaparotomy
1.	Choledocholithiasis		Tumor obstruction at ampulla		Carcinoma of pancreas
2.	Cholangitis vs pancreatitis		Gall stones, normal ducts		Cholelithiasis
3.	Carcinoma of pancreas	Large pancreatic mass	Tumor obstruction of CBD	No significant pathology	Carcinoma of pancreas
4.	Alcoholic hepatitis vs choledocholithiasis	Small shrunken liver	Normal	Alcoholic hepatitis	Alcoholic hepatitis
5.	Carcinoma of pancreas vs Thorazine cholestasis	Bile stasis, hepatomegaly	Stone obstructing CBD		Choledocholithiasis
6.	Retained stones		Smooth tapered obstruction of common bile duct		Post-cholecystectomy ligation of duct
7.	Carcinoma of pancreas		Partial tapered obstruction of common hepatic duct	Bile stasis	Carcinoma of hepatic duct
8.	Choledocholithiasis	Large pancreatic mass	Tumor deformity of CBD	Bile stasis	Carcinoma of pancreas
9.	Cholangitis vs metastatic disease	Dilated gallbladder	1 stone in CBD no visualization of G.B.		Choledocholithiasis
10.	Carcinoma of pancreas	Pancreatic mass	Tumor obstructing common duct		Carcinoma of pancreas
11.	Carcinoma of gallbladder		Irregular narrowing common hepatic duct Irregular wall of G.B.	Bile stasis	Carcinoma of G.B.
12.	Choledocholithiasis vs Thorazine cholestasis	Large bile stained liver	Stones obstructing common duct		Choledocholithiasis
13.	Metastatic disease	Multiple nodules in liver	Unsuccessful	Multicentric hepatoma	Hepatoma
14.	Carcinoma of pancreas		Stones in common duct		Choledocholithiasis
15.	Sepsis from cholangitis	Cirrhotic liver	Normal	Nutritional cirrhosis	Cirrhosis
16.	Cholangitis		Unsuccessful	Bile stasis compatible with extrahepatic obstruction	
17.	Cirrhosis	Metastatic disease	Unsuccessful	Metastatic breast cancer	Metastatic breast cancer
18.	Cholelithiasis		Normal sized duct with stones		Choledocholithiasis
19.	Carcinoma of pancreas	Metastatic disease	Normal extrahepatic ducts, diffuse involvement of intrahepatic ducts	Metastatic adenocarcinoma	Metastatic adenocarcinoma
20.	1° Biliary cirrhosis	Bile stained liver	Stones in bile duct	Chronic active hepatitis	Choledocholithiasis
21.	Choledocholithiasis vs hepatitis		Normal	Active hepatitis	hepatitis Hepatitis
22.	Extrahepatic obstruction vs metastatic disease	Normal liver, large pancreatic mass	Complete obstruction of CBD		Carcinoma of pancreas
23.	Carcinoma of pancreas	Bile stained liver	Obstructive CHD	Carcinoma of duct	Carcinoma of pancreas

cholangiogram was entirely normal. A diagnosis of intrahepatic cholestasis secondary to Gold therapy was made. In patient No. 23, cholangiography demonstrated obstruction of the common hepatic duct. This was interpreted as showing a carcinoma of the bile duct but the patient was surgically demonstrated to have a carcinoma of the pancreas.

Cholangiography was performed successfully in 20 of the 23 patients. Of the remaining three, there was only a perfunctory attempt at cholangiography in two (Nos. 13 and 17) because the diagnosis of metastatic carcinoma and multi-focal hepatoma was evident by direct observation and biopsy. The third patient was No. 16 mentioned

above. Normal biliary tracts were visualized successfully in three patients, two with hepatitis and one with cirrhosis. In addition, patient No. 2 was found to have normal ducts with a stone in the gallbladder, and another (No. 19) had diffusely constricted ducts secondary to metastatic disease. In the 8 cases in which the patient was either felt to have a non-surgical disease or in which the diagnosis was in question, 5 were proven to have cholelithiasis. In the others the precise diagnosis was changed although the therapy was not. In the 14 patients felt to have a high probability of surgical disease, three were saved surgery and the clinically determined etiology of the obstruction was proven incorrect in 4.

TABLE 2. *Factors Limiting Usefulness of Procedures for Visualization of the Bile Duct*

	PTHC	TPC	LTHC	ERC	OTHC
Allergy to contrast material	+	+	+	+	+
Presence of echinococcus cyst	+	+	+	—	+
Bleeding tendency	+	—	?*	?	—
Presence of ascites	+	—	+	—	—
Sepsis	?	?	?	—	?
Gall bladder required with patent cystic duct	—	—	+	—	—
General anesthesia needed	—	—	+	—	—
Incision required	—	—	+	—	+
Availability of operating room and patient in operable condition	+	—	+	—	—
Hepatitis or pancreatitis	—	—	—	+	—
Inability to leave catheter in place for drainage	—	—	—	+	—

* = Considered a contraindication by some authors

There were no wound complications and future surgery was not interfered with in any patient. There was no evidence of bile leak or hemorrhage. One patient (No. 2) ran a temperature to 38 C. Four of the patients with diffuse metastatic disease expired while still in the hospital. All were in poor condition prior to the procedure and continued to run a downhill course. One (No. 13) had undergone an angiogram the day prior to OTHC and subsequently went into renal failure, the cause of which was not clear but may have been related to the load of contrast material. Autopsies of three of the four patients (Nos. 11, 13 and 17) did not reveal any bile leak or hemorrhage. The fourth (No. 17) expired 2 weeks after the procedure. Consent for autopsy was refused.

Comments

Many factors influence the choice of diagnostic procedures for visualizing the biliary tree in cases of jaundice. Among these are the nature and accuracy of the information obtainable by each method, the relative risks involved in the procedures, the availability of facilities, the technical skills of the clinician and the expense to the patient. A summary of the limiting factors, the complications and the success rate for visualizing the ducts are listed in Tables 2, 3 and 4. The relevance of these

TABLE 3. *Complications of Procedures for Visualization of Bile Ducts*

PTHC	TPC	ERC	OTHC
Bile leak ^{10,12,14,22,26,31}	Bile leak ^{15,17}	Bile leak ^{4,5}	Bile leak ²⁸
Cholangitis, ^{22,31} fever	Fever ^{15,32}	Cholangitis ^{5,8,24,30}	Cholangitis ²⁸
Hemoperitoneum ^{22,31}	Phlebitis ¹⁷	Pancreatitis ^{5,18,21}	Hemoperitoneum ²⁸
Hemobilia ³¹	Atrial fibrillation ¹⁷	Elevated amylase ^{4,5,18}	Wound hematoma ⁷
Bilirubinemia ³¹		Pneumonia ²¹	Wound infection ²⁸
Puncture of other organs ^{10,26}			
Liver abscess ¹⁴		Pseudocyst ^{5,13,18}	
Death ^{19,31}		Death ¹	

TABLE 4. *Success Rate in Obtaining Cholangiogram by the Various Methods: Per Cent Successful Visualization*

Method	Bile Duct	Dilated Bile Duct	Normal Bile Duct
PTHC Weichel ³¹	72*		
Flemma ¹²	85		
Seldinger ²⁶	72*	92*	12*
Thorbjarnarson ²⁹	74	81	54
Ozdemir ²³	77		
Hines ¹⁶	78	93	41
Fleming ¹¹	68	89	22
Evans ⁹		92	43
Göthlin ¹⁴	82	96	50
Yu ³³		90	
Fischer ¹⁰	83	97	30
Okuda ²²	85		68
Weiner ³²	75	88	38
Kadell ¹⁷	65	85	22
LTHC Berci ²	100		
ERC Cotton ⁵	70*		
Robbins ²⁴	55		
Ogoshi ²¹	86		
Sáfrány ²⁵	78		
Dickinson ⁸	56		
Katon ¹⁸	73		
Blumgart ⁴	75		
Vennes ³⁰	85		
OTHC Strack ²⁸	88	100	66
Del Guercio ⁷			50
Stein ²⁷	88	100	75

*Compilation of many studies

considerations must be analyzed for each individual patient.

In general the minilaparotomy appears to have many advantages over the other procedures. Its one major disadvantage is the requirement of an incision. However, PTHC can be done safely only on patients who are surgical candidates and when an operating room is available. Elevated prothrombin time is a definite contraindication to PTHC, as are fever³ and ascites. LTHC requires both an operating room with general anesthesia and an incision. It can only be carried out in patients with both a gallbladder and a patent cystic duct. ERC is reported to be contraindicated in patients with hepatitis due to the inability to adequately sterilize the endoscope. Further, it is dangerous to attempt the procedure in patients with pancreatitis. The cost of the equipment and technical training for ERC²⁰ may be beyond the reach of the community hospital. Minilaparotomy, however, doesn't require extensive training and the equipment is available in all hospitals with image intensification fluoroscopy.

Complications from OTHC have generally been infrequent and of little consequence. Since it has become routine to suture the hole in the liver, the only complications reported have been rare wound problems. Multiple complications have been reported with the PTHC. In part they may be attributed to the large number of patients who have undergone this procedure since in the past it has been the most commonly employed. The complications have decreased since mandatory exploration for patients with obstruction has been instituted. Still there

are bound to be more complications with a blind procedure than an open one such as the OTHC. Peritoneal bile leak has been reported with both TPC and ERC, even though both were designed to prevent this complication. Cholangitis is a definite risk with ERC since a catheter is passed from a dirty to a clean partially obstructed bile duct. Elevated amylase is reported almost universally and deaths have also been reported after this procedure. There were no reported complications in the four patients who underwent LTHC.²

If the risks and disadvantages were universally small, the most important factor to consider in determining the indicated procedure would be the ability to arrive at the correct diagnosis. In the evaluation of biliary disease the OTHC with the minilaparotomy offers multiple diagnostic procedures and provides the best prospect of accurate diagnosis. About two-thirds of normal ducts have been visualized in the three reported series compared to 12% to 68% (median 45%) utilizing the PTH and only 22% to 38% with the TPC. Virtually all dilated ducts are visualized with the OTHC with slightly lower rates of visualization (80-95%) in the other procedure. It is difficult to compare the results directly with the LTHC and ERC. In the only report of LTHC all four attempts at cholangiography were successful. In the series reporting ERC most consider successful visualization when either the pancreatic duct or the bile duct is seen. However, when only considering those patients in whom liver disease is suspected and in whom the bile ducts are visualized, the success rate varies between 54% and 85% with most series reporting 60-80% success rate. The inability to visualize the duct cannot be used to differentiate surgical from medical jaundice since visualization is not related to the degree of dilatation of the duct. OTHC in addition offers the advantage of direct vision liver biopsy, palpation of organs, venography, etc. Using the combination of available modalities, the rate of successful diagnosis approached close to 100% in all three series.

The minilaparotomy has proven to be a safe reliable means of diagnosing the etiology of jaundice. Its overall accuracy in providing definite diagnostic information, its low complication rates and the minimal limitations of its use make it a most successful addition to the clinician's diagnostic armamentarium.

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A Review of Echinococcal Disease

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Echinococcal infestation, although still a rare occurrence in most of the United States, is being seen with increasing frequency. Three cases of hepatic echinococcosis are described. A review of the salient features of the disease is presented along with various aspects of diagnosis and therapy.

WITH THE ADVENT of more efficient and inexpensive means of transportation, increasing proportions of world populations are meeting and mixing. During the fiscal year ending June, 1973, slightly over 400,000 immigrants registered in the United States alone, approximately 6,500 of whom settled in Connecticut. With this migration, diseases uncommon in a particular region may appear with increasing frequency, thereby confronting the clinician with perplexing diagnostic and therapeutic problems. For example, in the last 3 years individual cases of echinococcosis originating in Greece, Italy and Hungary respectively were seen in the New Haven, Connecticut area. These cases are presented to reacquaint the physician with the salient features of this disease and the current modes of diagnosis and treatment; the major portion of this report will center around hepatic *Echinococcus granulosus* infestations.

Case Reports

(I.P., 816834) A 20-year-old Greek sailor entered the United States in early 1971. He presented with a right lower quadrant mass and vague epigastric pain, present intermittently for three months. He denied change in bowel habits, diarrhea, vomiting, weight loss, chills, fever, or jaundice. His vital signs on admission: blood pressure 108/70; pulse 84; and, rectal temperature 99.4 F. Pertinent physical findings were limited to the abdomen where a 6 cm in diameter mass was palpable to the right of the midline just above the pubis. It was freely movable, slightly tender to palpation with no pulsations or nodules. It was firm and felt to be intraperitoneal in origin. A suggestion of a similar mass was present

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under the right costal border. A third tender soft mass was felt anterior to the rectal wall at approximately 7 cm from the anal verge. Chest x-ray was within normal limits. Admission laboratory data included: hematocrit of 48%, WBC 10,100 with 59% segs, 1% bands, 0% eosinophils, bilirubin (total/direct) 0.33/0.11 mg %, SGOT 104 units, and alkaline phosphatase 32 units.

At laparotomy, multiple echinococcal cysts were found in the omentum, the perivesical and rectovesical spaces, the porta hepatis and posterior surface of the right diaphragm (Fig. 1). Most cysts had a stalk and were excised easily. Exposure of the diaphragm cyst was difficult and spillage occurred locally with its excision. The fluid contained many daughter cysts and the typical scolices were seen (Figs. 2 and 3). After removing the surrounding packs, the area was irrigated thoroughly with saline and a sump tube was left in place. There was no obvious primary intraperitoneal source that accounted for the initial seeding of cysts in this patient. His postoperative course was complicated by fever and a right lower lobe pneumonitis, treated with antibiotic therapy and pulmonary toilet. The patient refused further study or treatment after convalescence and returned to Greece on discharge.

(A.R., 100634) An 18-year-old Italian youth immigrated to the United States at the age of 10 years. His childhood was spent in rural Northern Italy where frequent contact with sheep, dogs, and other farm animals occurred. He was well until 5 days prior to admission when crampy, nonradiating right upper quadrant and epigastric pain developed. Two days later the patient had a shaking chill and a temperature of 102 F orally but denied nausea, vomiting, change in bowel habits or jaundice. Several similar painful episodes had occurred within the last year but were self limited and required no treatment.

On admission his blood pressure was 130/86 with a pulse of 70 and a rectal temperature of 99.8 F. There was no scleral icterus, jaundice, or cutaneous malformation. Dull tenderness without guarding or rebound was present in the right upper quadrant and a smooth, nontender liver edge was palpable 3 cm below the right costal border.

Admission laboratory data: hematocrit 48%, WBC of 11,300 with 34% eosinophils (on repeat - 49%), prothrombin time (control/patient) 13/17 seconds, total bilirubin 1.1 mg %, BSP retention 8%, alkaline phosphatase 74 units, SGOT 26 units, SGPT 138 units, and LDH 380 units. The echinococcus indirect hemagglutination titer was 1:35,600 (diagnostic level 1:800) and the bentonite flocculation titer read 1:5,120 (diagnostic 1:800). Multiple fresh stools for ova and parasites were

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FIG. 1. Hydatid cyst with its stalk removed from the porta hepatis of patient number one.



negative. Chest x-ray, UGI series and oral cholecystogram were within normal limits. A liver scan demonstrated a concavity on the inferior border of the liver. The right upper quadrant pain worsened and a temperature spike of 104 F occurred. At laparotomy, multiple, pale-pink fluctuant, 3-4 inch in diameter abscess cavities were found in the left lobe of the liver. Thick, brown purulent material was aspirated from these cavities which were then irrigated with saline and packed with iodoform gauze. Cultures of the abscesses grew alpha *Streptococci*, *Pneumococci* and *Bacteroides* species. Type specific antibiotics were given and the iodoform pack was gradually removed without incident. Pathological examination of the material removed at surgery confirmed echinococcal disease.

(J.K., 041 32 9365) A 35-year old Caucasian man of Hungarian nationality was forced to scavenge food from garbage piles to survive the

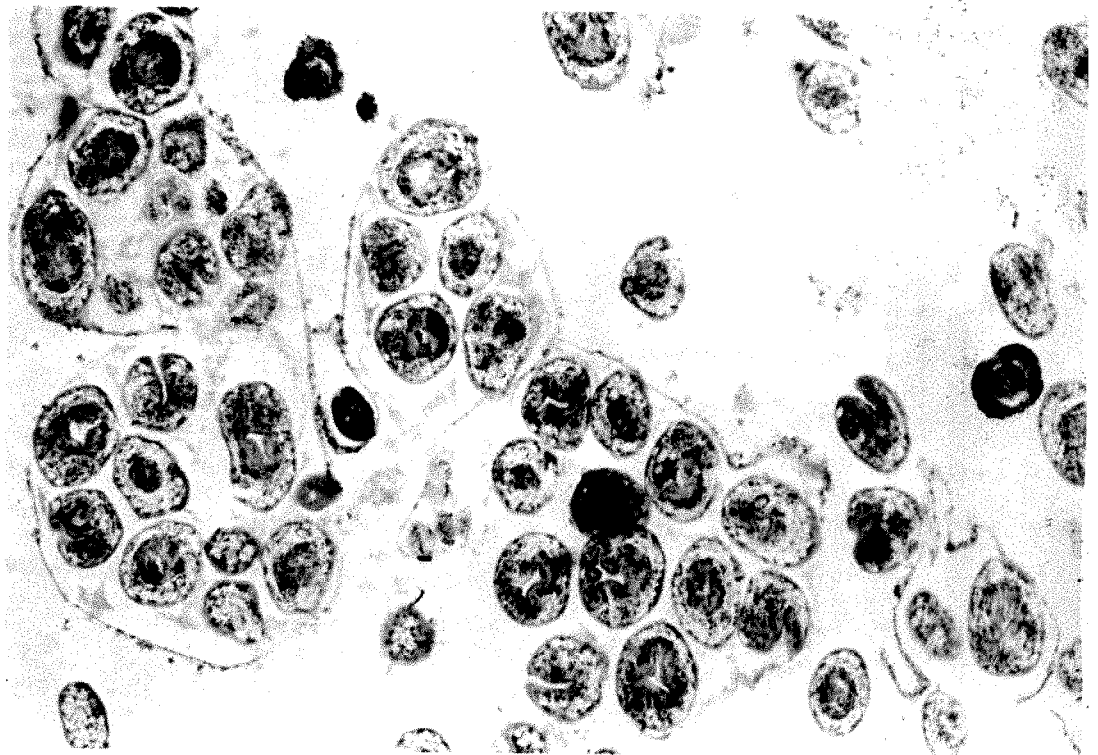
rigors of World War II. Later, as a teenager, he worked as a shepherd in Hungary where many of his sheep died from an unknown disease. In 1956, he emigrated to the United States and was essentially asymptomatic until postprandial epigastric and right upper quadrant colicky pain developed 16 years later. An oral cholecystogram was within normal limits and an UGI series showed a small hiatal hernia at this time. A bland diet did not relieve the pain which actually worsened over the next three months and became associated with nausea, vomiting, and jaundice. These symptoms cleared spontaneously, but recurred two months later. On admission to the West Haven VA Hospital, the patient was acutely ill with upper abdominal pain. His blood pressure was 120/80, the pulse 68 and the temperature 99.6 F rectally. The sclera and skin were nonicteric and examination of the head, neck, and chest revealed no abnormalities. Marked right upper quadrant tenderness with voluntary guarding was present but no signs of peritoneal irritation could be elicited. No masses or organomegaly were present and brown guaiac negative stool was found in the rectum.

Admission laboratory data included: hematocrit 44%, WBC 4,900 with 53% segs, 0% bands, and 5% eosinophils, bilirubin (total/direct) 4.5/3.1 mg %, alkaline phosphatase 190 units (normal 30-85), SGOT 16: units (normal 10-50), normal amylase and lipase. Chest x-ray and KUB were normal and an UGI series confirmed a small sliding hiatal hernia. Neither oral nor intravenous cholangiography showed any visualization of the biliary tract.

At laparotomy numerous adhesions were found around the gallbladder and in the porta hepatis. The liver was felt to be normal, but the common bile duct was dilated to a diameter of approximately 2-2.5 cm. A cholecystectomy was performed, but no stones were found. Upon opening the common bile duct, green-white tissue strands were extruded and further material was removed by irrigation. Pathologic examination of this material revealed echinococcal scolices (Fig. 4). A T-tube cholangiogram demonstrated material in the distal duct that was extracted with forceps (Fig. 5). Intrahepatic biliary radicles in the right lobe of the liver were distended but no definite space-accompanying mass could be delineated by operative cholangiography. After copious irrigation of the operative area, the abdomen was closed.

A postoperative liver scan (Fig. 6) showed a defect in the right lobe and an hepatic arteriogram demonstrated a mass lesion deep within the anterior segment of the right lobe (Fig. 7). Multiple samples of T-tube

FIG. 2. Hydatid fluid from cyst in Fig. 1. Daughter cysts are seen with their surrounding membranes intact ($\times 208$).



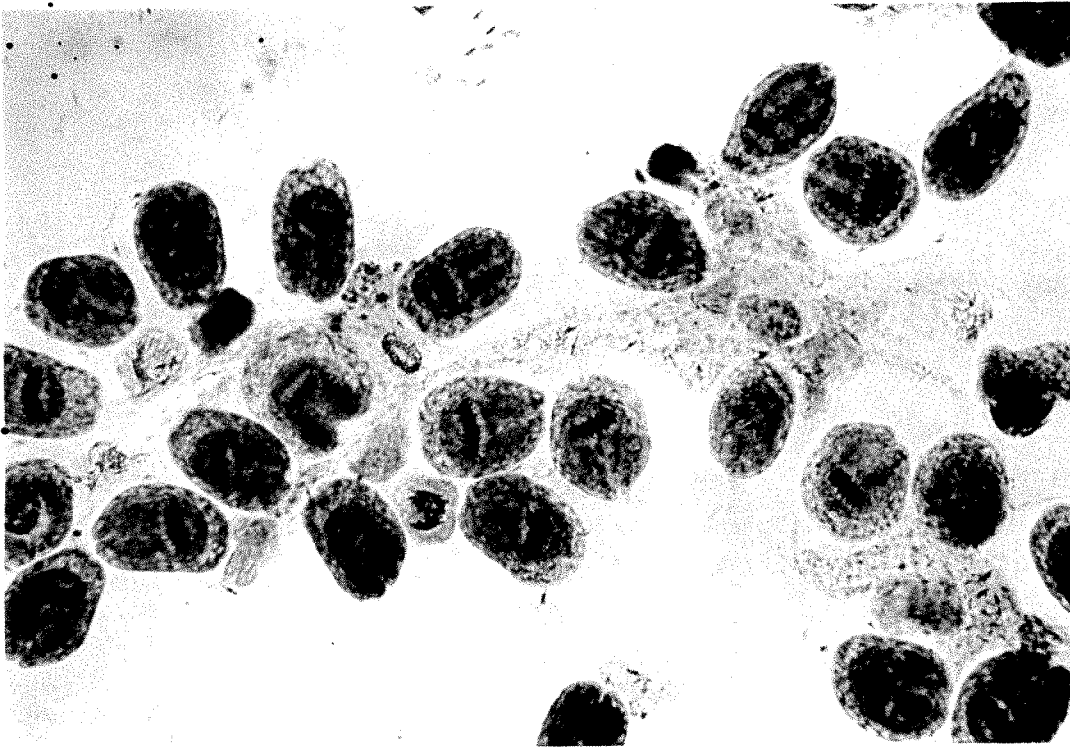


FIG. 3. Giemsa staining brings out the scolices in the hydatid fluid ($\times 208$).

aspirate showed no scolices or other hydatid material. The indirect hemagglutination titer was 1:1024 (diagnostic level 1:32) and the bentonite flocculation was negative.

One month later, the liver was re-explored; no mass lesion was palpable. After extensive packing of the operative area, a spinal needle was introduced into the anterior segment of the right lobe of the liver and approximately 35 cc of a dark, bile-stained fluid were aspirated. Absolute alcohol (95%) was injected into the cavity while isotonic

saline was gently irrigated through the T-tube into the common bile duct to prevent injury to the ductal system. The alcohol was removed after 10 minutes and an incision was made in the right lobe of the liver and the cyst wall was identified and excised. The resultant cavity (estimated volume — 50 cc) was swabbed with absolute alcohol and an omental pedicle was sutured into place to obliterate the dead space and allow absorption of any exudate. An operative cholangiogram showed debris in the common bile duct which was then removed through the original

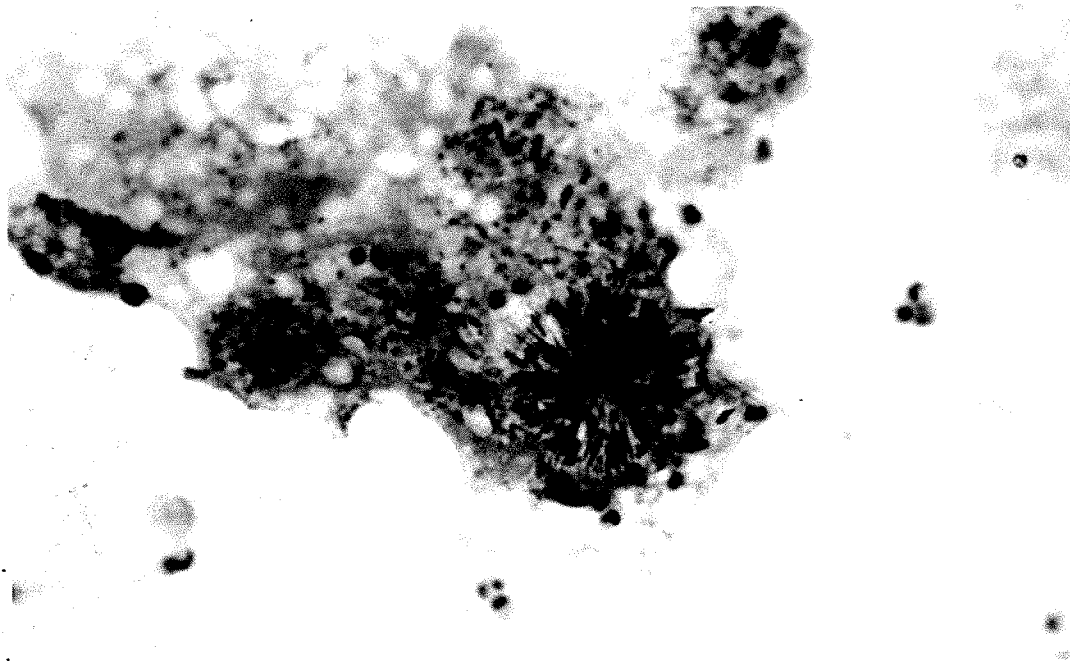


FIG. 4. Microscopic examination ($\times 334$) of material from the common bile duct of Patient number three. The typical scolex can be seen under high power.



FIG. 5. Gross appearance of material extracted from distal common bile duct of Patient number three.

choledochotomy. A second cholangiogram following reinsertion of the T-tube showed the site of communication of the cyst with the biliary tree but no further intrabiliary material was seen (Fig. 8). The post-operative course was uncomplicated and a repeat T-tube cholangiogram 2 months later was normal. The T-tube was, therefore, removed. The patient remains symptom free at two years and the indirect hemagglutination test has become negative (Fig. 9).

Occurrence

Echinococcus has a world-wide distribution with heaviest infestations in regions of cattle and sheep husbandry, e.g., Central Europe, South America and eastern Australia. In North America the largest endemic area is

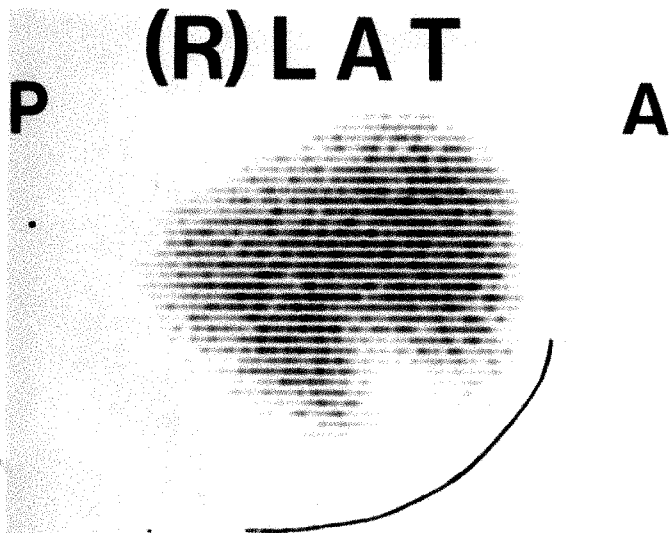


FIG. 6. Right lateral view of liver scan on Patient number three following first operation. This demonstrates a single filling defect in the anterior segment of the right lobe.

Alaska with an estimated 22% infestation rate in dogs in certain areas.¹⁶ In the Yukon territory alone, up to 40% of the indigenous human population is infested.³ It is also seen in southwestern Canada and adjacent U.S. states, California,¹¹ the mid-southern states and Mexico.²³ The first demonstration of the complete cycle of transmission of *Echinococcus granulosus* in the United States occurred in 1969, in the Central Valley of California.¹⁸ In various parts of Italy, 50-90% of slaughtered cattle harbor the disease.²⁰ In Greece, the annual human morbidity is 7.5 individuals per 100,000²² and in adjacent Adriatic zones, up to 30% of sheep are infested.²¹ Other heavy endemic areas are the western coast of South America, Spain, Portugal, adjacent North African states, mid-eastern Africa, Iraq, southern India, Russia, and eastern Australia.

Parasitology

The word echinococcus originates from the Greek meaning "hedgehog berry," a term descriptive of the gross pathology of the lesion. Another descriptive Greek word applied to this disease is hydatid, "a drop of water." This disease process probably was known to Hippocrates who described, "liver(s) . . . filled with water."¹ The etiologic agent and its characteristics were delineated during the 17th and 18th centuries, but the complete life cycle was not documented until the 19th century.

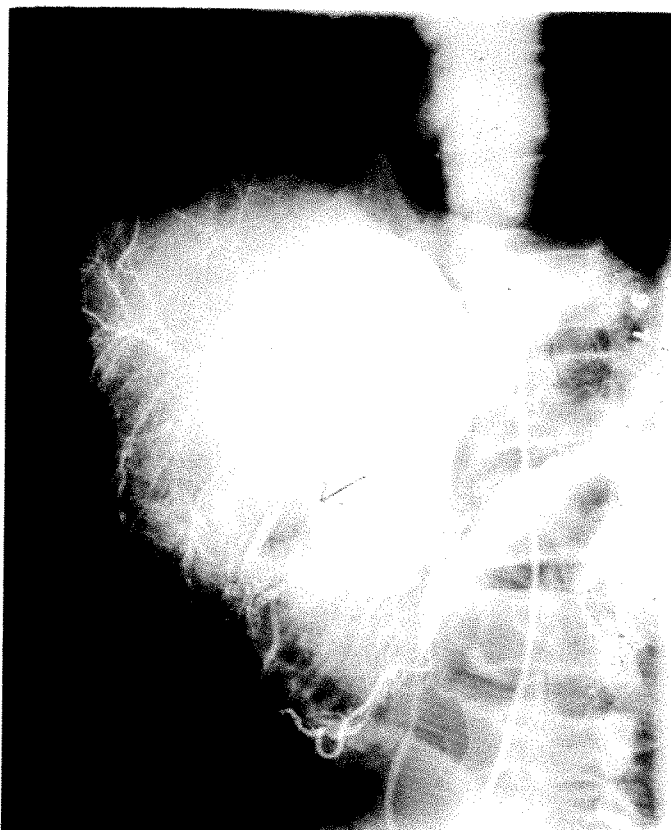


FIG. 7. Hepatic arteriogram on Patient number three showing location of cyst in the liver.

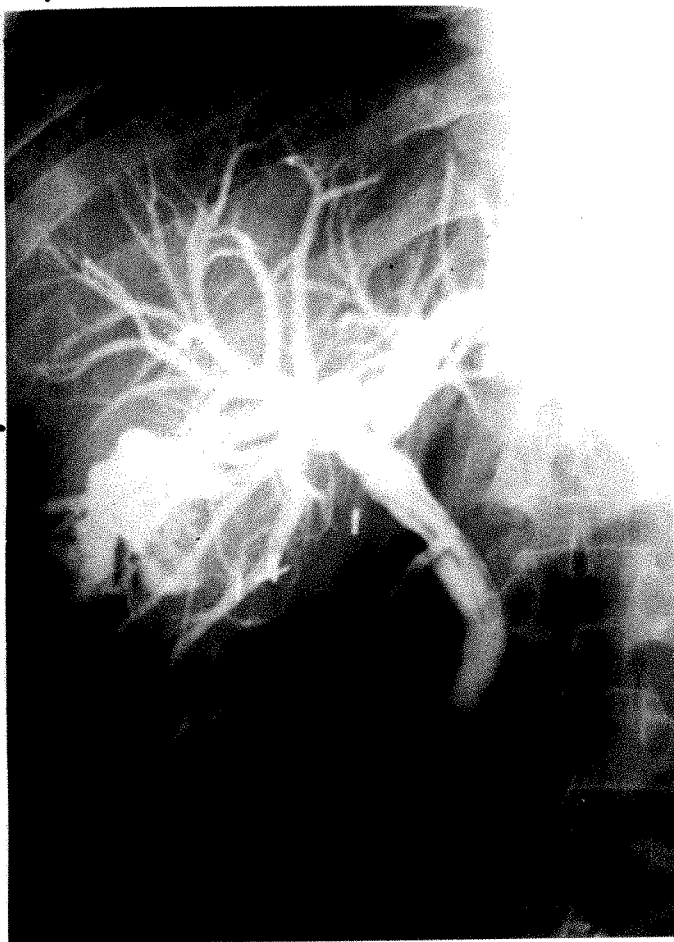


FIG. 8. Intra-operative cholangiogram during second procedure on Patient number three. The cyst fills from the biliary tree, but no material is seen in the biliary tract.

The definitive hosts for *Echinococcus granulosus* are dogs, wolves, foxes, and other sylvatic carnivores. This tape worm, usually 4-6 mm in length, lives attached to small bowel villi and the infective ova are shed through the feces. When swallowed by intermediate hosts such as man, sheep, cattle, or hogs, the embryo passes through the intestinal wall and enters the portal circulation, eventually reaching the liver. Most embryos are trapped in the liver, but some pass through the microcirculation to the lungs and rarely to other parts of the systemic circulation (Fig. 10 shows a large calcified echinococcal cyst of the spleen in an elderly physician who was unaware of its presence for many years. There was no evidence of any other systemic involvement.)* Regardless of the location, the embryo enlarges into a tiny cyst which then develops several layers. The germinal epithelium, which produces broad capsules and eventually the scolices, is the active portion of the cyst. A highly antigenic fluid, *eau de roche*, also collects within the cyst cavity and daughter cysts often are found floating therein. (In patient J. K. the echinococcal cyst ruptured into the biliary tree

and daughter cysts impacted in the ampulla of Vater producing obstructive jaundice.) The life cycle is completed when the definitive hosts (dogs, wolves, foxes) consume the infested viscera of the intermediate host. A more detailed summary of hydatid morphology and life cycle can be found in standard parasitology textbooks.

Clinical Features

The liver is the most frequently parasitized organ in the human with an infestation rate of approximately 60% followed by the lung with 30% involvement.¹⁷ The remaining fraction is scattered throughout the body with no particular organ system predominating. Since the echinococcal cyst grows slowly, symptoms may not appear for many years until adjacent structures are compressed or deformed producing pain or organ system dysfunction. With hepatic involvement, approximately 75% of cysts are located in the right lobe¹⁷ where they may grow to enormous sizes containing up to 16 liters of hydatid fluid.⁵ The patient may accidentally discover an asymptomatic abdominal mass or present with right upper quadrant pain. Many cases are documented following a complication of the initially asymptomatic infestation. Rupture of the cyst into the biliary tract may occur in 5-10% of cases with hepatic involvement.^{12,14} This usually presents a clinical picture compatible with choledocholithiasis and cholangitis including colicky right upper quadrant pain, jaundice and fever when secondary infection occurs. The finding of daughter cysts or scolices in the stool or vomitus will confirm the diagnosis. Urticaria and peripheral eosinophilia may be present due to the strongly antigenic nature of the cyst fluid.

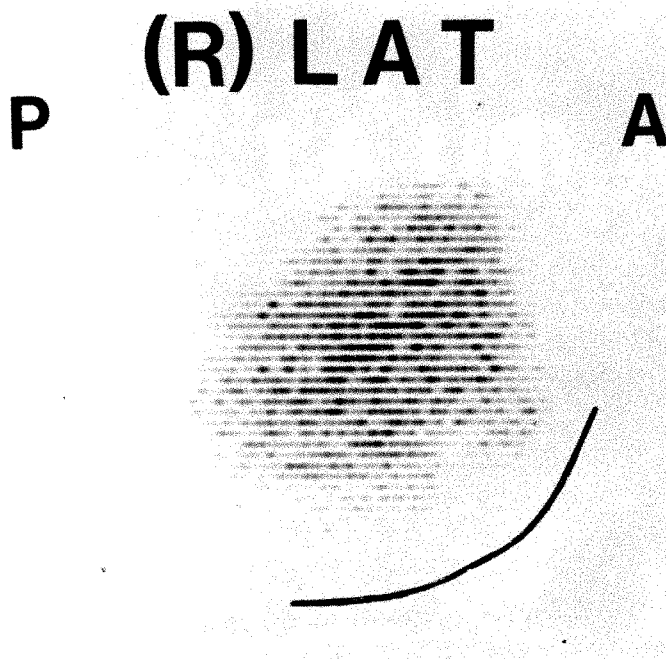


FIG. 9. Right lateral view of liver scan 2 years after first procedure on Patient number three. The defect appears less distinct at this time.

*This patient is not included as a case report because we have no other documentation of the disease besides the classic radiologic picture.

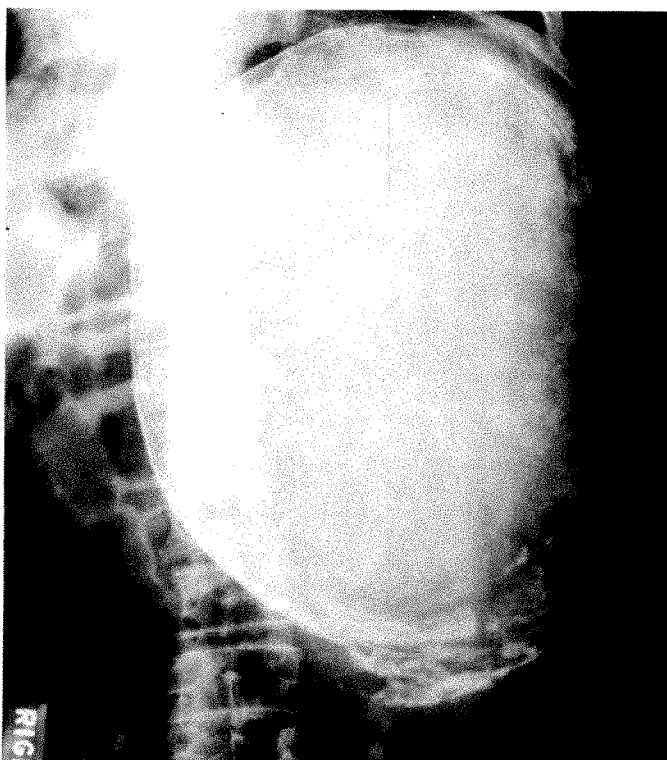


FIG. 10. Abdominal roentgenogram showing huge calcified echinococcal cyst of the spleen.

Secondary pyogenic infection of the cyst may occur without direct communication with the biliary tract. Chills, fever, and right upper quadrant tenderness, with or without a mass will be present. Cysts may rupture into the free peritoneal cavity producing peritonitis and metastatic seeding. In a review of 223 cases of hydatid disease, 30 instances of peritoneal spillage at the time of surgery were documented.¹⁹ Positive evidence of secondary cyst growth was found in only 4 of these 30 patients; 3 out of the 4 were followed greater than 5 years. Rupture through the dome of the liver can produce a subdiaphragmatic abscess which may penetrate into the contiguous pleural space or pulmonary parenchyma.⁷ Daughter cysts may be coughed up if erosion into the bronchial tree occurs. Since the hydatid fluid is highly antigenic, spillage beyond the confines of the cyst may result in a severe anaphylactic reaction with circulatory collapse and death. In 5-10% of cases the cyst will die and eventually calcify.¹⁰ This may be caused by rupture into the biliary tree with expulsion of all infective material, hemorrhage into the cyst, or secondary infection of the hydatid cavity.

Laboratory Diagnosis

Since many of the symptoms and signs of echinococcosis are nonspecific and only suggestive, laboratory examinations have been devised to aid the clinician in establishing a diagnosis. The immunologic response of

the host to the strongly antigenic nature of the hydatid fluid forms the basis of several determinations. Injection of human and animal hydatid fluid into the dermis of an infested patient is the basis of the Casoni test. An urticarial papule will develop in 59-70% of cases but may also be positive in carcinomatosis, leishmaniasis and teniasis.^{2,17} The indirect hemagglutination test for hydatid disease has a much higher specificity and a diagnostic titer virtually confirms the diagnosis. However, negative results may be recorded in up to 35% of patients with pathologically confirmed disease.² A complement fixation test, similar to the Wasserman reaction, is available and is positive in up to 80% of patients with the disease.¹⁷ Recently, immunoelectrophoretic tests have been devised that will give up to 93% positive results in proven cases of hydatid disease. The association of at least two tests (the indirect hemagglutination and immunoelectrophoretic assays) will result in laboratory diagnosis of over 94% of all cases.⁴

When the cyst dies or is completely removed surgically, the hemagglutination and complement fixation tests (and occasionally the Casoni reaction) will revert to negative thus affording some prognostic significance. Due to the relatively recent development of specific immunoelectrophoretic determinations for echinococcosis, it is not known whether titers will fall with cyst death.

Eosinophilia, although nonspecific, may be seen in approximately 50% of cases ranging usually between 5-10% of the white cells counted.²

Scintillation scans of the liver, spleen, bone, and brain may suggest a space occupying mass that can be further defined by selective angiography. These modalities proved especially helpful in Patient J.K. whose cyst could not be detected by inspection or palpation during the initial laparotomy.

Treatment

Although screening programs for scolical drugs exist,⁶ to date no effective medical treatment is available and surgery remains the best hope for cure. Effective treatment requires accurate preoperative assessment of the extent of disease and its state of antigenicity. Small calcified cysts of the liver with negative serologic tests need no specific treatment. Suspicion of active disease should be confirmed by serologic examinations and localization accomplished by radioactive scans and selective arteriography. Percutaneous aspiration of cysts in suspected Echinococcosis should not be performed under any circumstance since dissemination or anaphylaxis can occur. Since manipulation or spillage of the highly antigenic cyst fluid at the time of operation also can cause anaphylactic shock, anesthesia personnel should be fully acquainted with this complication with provisions made for specific treatment if a shock state should develop. The intravenous administration of pres-

sors such as epinephrine or aramine to counter the massive peripheral vasodilation coupled with a beta adrenergic agent such as isoproterenol to reverse bronchospasm if present will result in the highest salvage rate.⁹ The value of large doses of intravenous steroids is unclear, but probably is beneficial.

If the cyst is large or multicentric within one anatomic unit of the liver, hepatic lobectomy is the procedure of choice.¹⁵ All contiguous structures should be meticulously isolated from the infective material by gauze packs and lobectomy is performed in the standard manner. A different procedure should be employed if a single small cyst in one lobe or several cysts in multiple lobes are found. Again extensive packing of the operative field should be done. If the cyst is not readily visible or palpable, a spinal needle on an aspirating syringe should be introduced into the most likely area demonstrated by preoperative scans and arteriography. Care should be taken with aspiration since the hydatid fluid can be under increased pressure with the chance of dissemination. All fluid should be removed and replaced with an equal volume of a substance toxic to the *Echinococcus*, such as hypertonic saline (15-20% solution), absolute alcohol, hydrogen peroxide, or certain other solutions.⁸ Formalin, which used to be the preferred agent, has been discontinued by most surgeons because of the occasional fatality associated with its use. When the contents of the cyst are bile-stained, one should not use any caustic substances for injection. The material chosen should be left in the cyst cavity for at least 5-10 minutes and all debris and daughter cysts should be removed thereafter. The resultant defect can be managed in several ways. Marsupialization was used extensively in the early treatment of this disease and consisted of suturing contiguous portions of the wound edge to the walls of the cyst cavity. It invariably resulted in a chronically draining wound often with biliary fistulae and should be used only as a last choice when no other alternatives are feasible. *Capitonnage* has been used extensively in countries where echinococcosis is endemic.¹⁷ The superficial portion of the cyst is excised after sterilization and the remaining walls are brought together with a series of purse-string or mattress sutures starting from the bottom and working outward. As an alternative, a portion of omentum with a good blood supply can be sutured into the defect to accomplish the same obliteration of dead space.¹³

If the cyst is infected at the time of surgery, large drains should be placed into its depths and brought out through stab wounds. A drainage catheter can also be placed to allow irrigation of the cyst in the postoperative period. Omentum, if available can be used to help wall-off the infected operative area. If the cyst has ruptured

into the biliary system, T-tube drainage of the common bile duct should be considered following treatment of the primary hepatic locus.¹⁴

Acknowledgment

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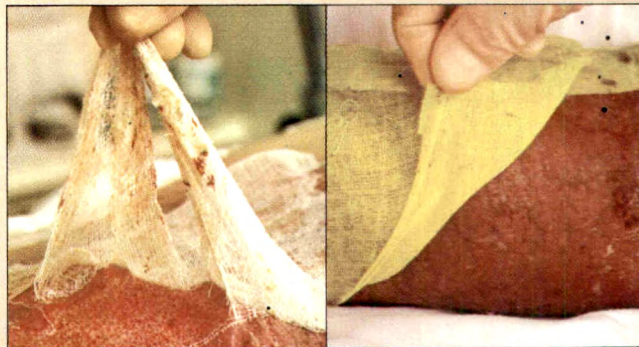
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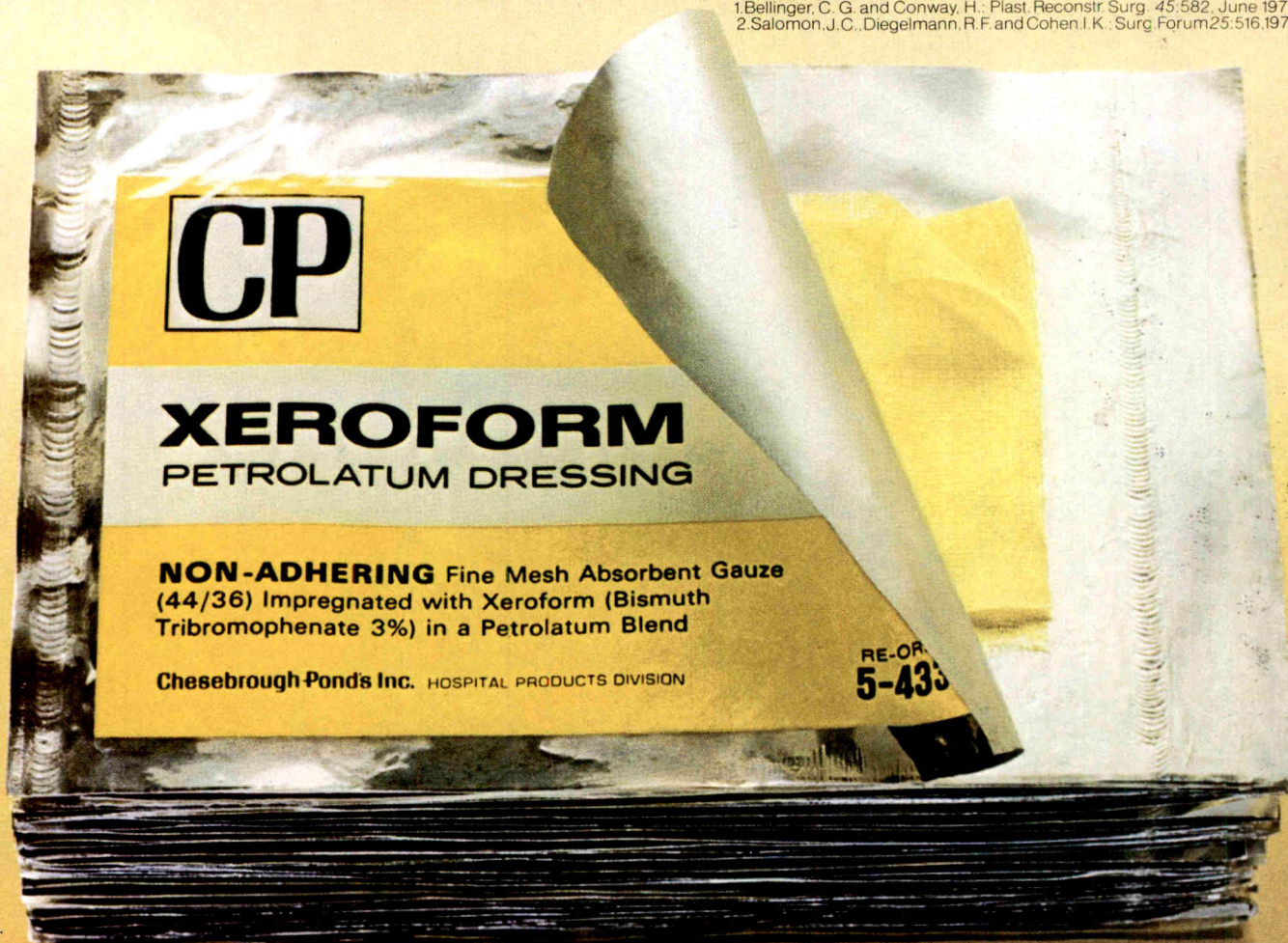
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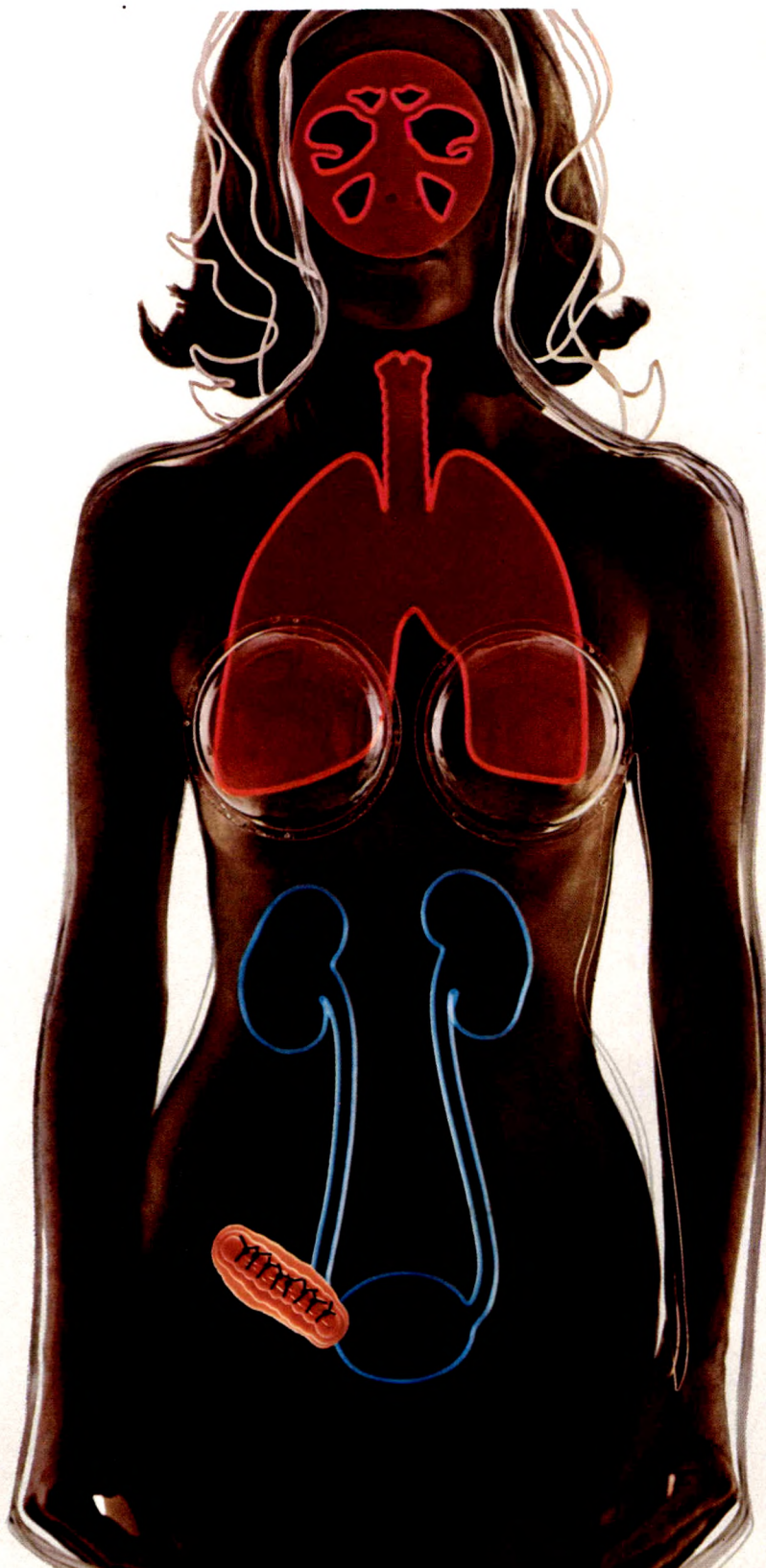
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Skin and soft-tissue infections caused by staphylococci.

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae*, *H. influenzae* and staphylococci.

Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

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'Anspor' is contraindicated in patients with known hypersensitivity to the cephalosporins. In penicillin-sensitive patients, cephalosporin C derivatives should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.

Adverse Reactions

The following adverse reactions have been reported: glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn; mild urticaria or skin rash, pruritus, joint pains; transient eosinophilia, leukopenia, neutropenia; transient rise of SGOT, SGPT, total bilirubin, BUN; dizziness, tightness in the chest, and candidal vaginitis.

For a brief summary of prescribing information, including indications, contraindications, warnings, precautions, adverse reactions, and dosage, please see the following page.

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DESCRIPTION

Anspor (cephradine, SK&F) is a semi-synthetic cephalosporin antibiotic chemically designated as 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl) acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephadrine is active against the following organisms *in vitro*:

Beta-hemolytic streptococci	<i>Diplococcus pneumoniae</i>
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains	<i>Escherichia coli</i>
	<i>Proteus mirabilis</i>
	<i>Klebsiella</i> sp.
	<i>Hemophilus influenzae</i>

Note—Some strains of enterococci (*Streptococcus faecalis*) are resistant to cephadrine. It is not active against most strains of *Enterobacter* sp., *Pr. morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephadrine and methicillin-type antibiotics.

INDICATIONS

Anspor (cephadrine, SK&F) is indicated in the treatment of the following infections when caused by susceptible strains of designated microorganisms.

Infections of the respiratory tract (e.g., tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and *D. pneumoniae*.

(Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Anspor' is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of 'Anspor' in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae*, *Hemophilus influenzae* and staphylococci.

Infections of the skin and soft tissues caused by staphylococci.

Infections of the urinary tract, including prostatitis, caused by *Escherichia coli*, *Pr. mirabilis*, and *Klebsiella* species.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Anspor (cephadrine, SK&F) is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary.

Usage in Pregnancy and Lactation: Safety of this product for use in pregnancy has not been established. Cephadrine is secreted in breast milk during lactation.

PRECAUTIONS

Follow patients closely to detect side effects or unusual manifestations of drug idiosyncrasy. If hypersensitivity reaction occurs, discontinue drug and treat patient with usual agents, e.g., pressor amines, antihistamines, or corticosteroids.

Administer with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy as cephadrine accumulates in the serum and tissues. See **DOSAGE AND ADMINISTRATION** section for information on treatment of patients with impaired renal function.

Prolonged use of antibiotics may promote the overgrowth of non-susceptible organisms. Take appropriate measures if superinfection occurs during therapy.

After cephadrine therapy, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®.

A positive Coombs test may be due to the drug.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: Glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn.

Skin and Hypersensitivity Reactions: Mild urticaria or skin rash, pruritus, and joint pains.

Blood: Mild, transient eosinophilia, leukopenia and neutropenia.

Liver: Transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage.

Renal: Transitory rises in BUN. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine.

Other adverse reactions have included dizziness and tightness in the chest and candidal vaginitis.

DOSAGE AND ADMINISTRATION

Anspor (cephadrine, SK&F) may be given without regard to meals.

Adults: For skin and soft-tissue and respiratory tract infections (other than lobar pneumonia), the usual dose is 250 mg. q.i.d. in equally spaced doses. For acute infections of the urinary tract, including prostatitis, and pneumococcal lobar pneumonia, the usual dose is 500 mg. q.i.d. in equally spaced doses; severe or chronic infections may require larger doses.

Children: The usual dose is 25 to 50 mg./kg./day total, q.i.d. in equally divided and spaced doses. For otitis media due to *H. influenzae*, doses from 75 to 100 mg./kg./day in equally divided and spaced doses are recommended. Maximum dose should not exceed 4 grams per day.

All patients, regardless of age and weight: Larger doses (up to 1 gram, q.i.d.) may be given for severe or chronic infections.

In patients with impaired renal function, a modified dosage schedule is necessary. Consider each patient individually utilizing the following guideline: In adults, initial loading dose is 750 mg. and maintenance dose is 500 mg. at following time intervals: creatinine clearance >20 ml./min., 6-12 hours between doses; creatinine clearance 15-19 ml./min., 12-24 hours between doses; creatinine clearance 10-14 ml./min., 24-40 hours between doses; creatinine clearance 5-9 ml./min., 40-50 hours between doses; creatinine clearance <5 ml./min., 50-70 hours between doses. Further modification may be necessary in children.

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Precautions: Do not administer to children under two years of age unless directed by a physician.

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Lynchburg, Va. 24505

Studies on Bile Salt Deconjugation Following Small Bowel Bypass Procedures

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Using the glycine-1-¹⁴C-cholic acid (¹⁴C-GCA) test, bile salt deconjugation and excretion were studied in 26 subjects with morbid exogenous obesity before and at selected intervals after jejuno-ileal bypass. In the preoperative group there was no malabsorption or intestinal bacterial deconjugation of the bile salts. In the immediate postoperative period (with relative sterilization of the bowel) there was only a trace of ¹⁴C in the breath, but the fecal ¹⁴C was highly elevated, indicating severe malabsorption without bacterial activity. In the 8 to 10 day postoperative period both the breath and fecal ¹⁴C content were highly elevated, indicating malabsorption and normal bacterial activity. Five to 8 months postoperatively both the breath and fecal ¹⁴C content showed only moderate elevation, indicating adaptation. It is suggested that the ¹⁴C-GCA test is useful in evaluating the adequacy of small bowel bypass procedures and also in following the adaptive response after the bypass. A significant increase in the breath and fecal ¹⁴C soon after surgery followed by rapid decrease suggests an adequate bypass and unusually fast adaptation. If the increase in the breath and fecal ¹⁴C soon after the bypass is only moderate, then that suggests an inadequate bypass.

THE MAJOR BILE ACIDS synthesized in the human liver are cholic acid and chenodeoxycholic acid (primary bile salts); they are present in bile as the sodium and potassium salts, conjugated to glycine or taurine. In response to meals, these conjugated bile acids are secreted into the duodenum. Conjugated bile salts play a vital role in the emulsification, hydrolysis, and absorption of lipids. Under normal circumstances most of the conjugated bile salts are absorbed by active transport in the terminal ileum; then they are reexcreted in bile and are again reabsorbed, and this continuous cycle is termed the enterohepatic circulation of bile salts.⁴ A small fraction of the conjugated bile salts passes into the colon, where it is deconjugated by bacterial enzymes and it is either absorbed or it is excreted as free acid in the stool. In normal subjects the bile salt pool remains fairly constant, the

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small amount of fecal loss being balanced by hepatic synthesis from cholesterol.^{3,8}

The purpose of this study was to evaluate the amount of bile salt deconjugation and malabsorption following small bowel bypass procedures, and to assess the role of the ¹⁴C-GCA test in the evaluation of the intestinal adaptive response and the adequacy of the bypass.

Materials and Methods

The studies were performed at the Clinical Research Center in Barnes Hospital. Twenty-six patients with morbid exogenous obesity were studied before and at selected intervals after jejuno-ileal bypass. The type of bypass performed is represented diagrammatically in Fig. 1. In this procedure, 35 cm of proximal jejunum is anastomosed end-to-end to 10 cm of terminal ileum. The intervening segment of small bowel is excluded; the proximal end of this segment is then closed and the distal end is anastomosed end-to-side to the cecum. The preoperative ¹⁴C-GCA (Glycine-1-¹⁴C-cholate) studies were performed about a week prior to operation; the postoperative studies were performed 3 to 4 days following operation (during a period when these patients were receiving parenteral Keflin), 8 to 10 days following operation (when the patients were not receiving antibiotic therapy), and finally, 5 to 11 months postoperatively.

Glycine-1-¹⁴C-cholate was given orally to these subjects and the ¹⁴CO₂ specific activity of expired air was measured by a breath-analysis technique. The amount of ¹⁴CO₂ in the expired air is an index of the bacterial deconjugation of ¹⁴C-GCA.¹⁵ The ¹⁴C content of a 48 hour stool specimen following the ingestion of ¹⁴C-GCA was also measured, and this is an index of malabsorption.

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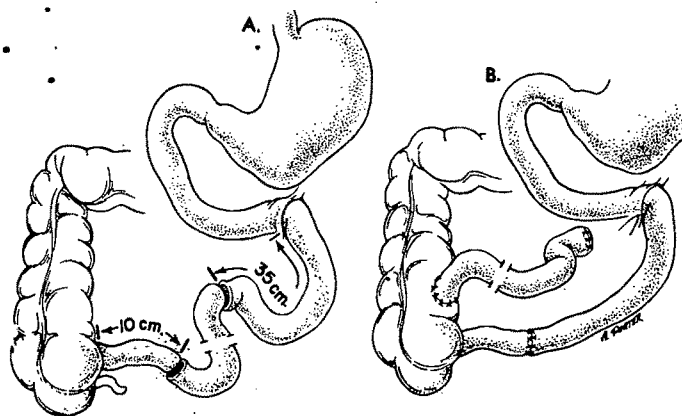


FIG. 1. Small bowel bypass procedure as performed by the authors.

Glycine-1- ^{14}C -cholic acid, sodium salt, specific activity of approximately 19 mCi/mmole was purchased in 250 μCi quantities (from Radiochemical Centre, Amer-sham). It was dissolved in absolute ethanol so that 10 μCi was contained in 0.5 ml solution. A control breath analysis was performed in each patient prior to the administration of 10 μCi of the conjugated bile acid which was given in the fasting state at 8:00 am. Four further breath analyses were then performed at two hour intervals, and a final analysis was done 24 hours after the administration of the bile salt. The patients received no food until after the noon test, but had breakfast prior to the 8:00 am test the following morning.⁵ During the test periods the patients were instructed to exhale normally and then blow the residual air over a drying tube containing silica gel into a counting vial containing the trapping solution. The trapping solution consisted of 4 ml of a 0.5 molar solution of hyamine hydroxide in methanol:ethanol (1:1) and thymolphthalein as the indicator of the completion of the neutralization and the trapping of 2 mmole CO_2 . The exact quantity of CO_2 collected was determined by titration of the hyamine stock solution with hydrochloric acid. The specific activity of the $^{14}\text{CO}_2$ in the vial was measured by liquid scintillation spectrometry after the addition of a toluene based scintillation cocktail.

Results were expressed as a percentage of administered dose per mmole of CO_2 , with the assumption that the average CO_2 in expired air is 9 mmole per kg body weight per hour.^{5,9} Such correction for weight is important, since the greater the endogenous CO_2 production the lower the specific activity.¹

Fecal ^{14}C was measured in 48 hour stool collections. Samples were homogenized with a blender (Lourdes Instrument Co.); additional water was added, when required, to liquify the fecal matter. Three aliquots were removed from the homogenized sample, were remixed with a Vortex mixer (Scientific Products Co.) and were applied on a 4×4 cm desiccated filter paper, Whatman No. 42 (W & R Balston Limited, England), and weighed before and after vacuum desiccation. The three aliquots varied less than 10% (dry weight/wet weight) gravimetrically. Sample ^{14}C was collected by the oxygen flask combustion method (Packard 305 Sample Oxidizer, Packard Instrument Co., U.S.A.), and estimated by a liquid scintillation counter (Packard 3380, Packard Instrument Co.) using external standardization.

The radiation exposure associated with the ^{14}C -GCA breath test is less than 0.4 m rad on the date of test as compared to a 5 m rad gonadal exposure from a chest roentgenogram.⁹

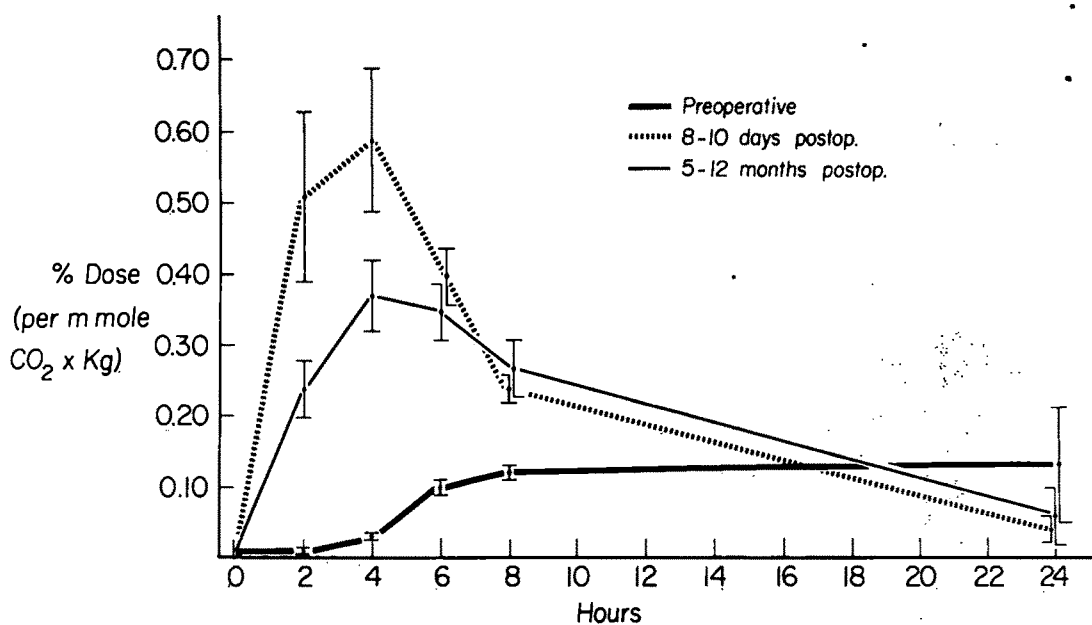
Results

In Table 1 the time course of $^{14}\text{CO}_2$ excretion in the breath after the administration of ^{14}C -GCA is recorded. During the preoperative control period the subjects excreted very little $^{14}\text{CO}_2$ up to 6 hours and even then in most subjects the excretion did not rise above 0.1% dose/mmole $\text{CO}_2 \times \text{kg}$ body weight. In the immediate postoperative period (while on antibiotic therapy) there was no measurable $^{14}\text{CO}_2$ in the breath. Eight to 10 days postoperatively, however, there was a significant increase in the amount of $^{14}\text{CO}_2$ in the breath. All patients had very high excretion within 2 hours and this increased excretion persisted for about 8 hours; by 24 hours there was only minimal excretion of $^{14}\text{CO}_2$. Five to 10 months after operation again there was a significant increase in

TABLE 1. Time Course of $^{14}\text{CO}_2$ in Breath After the Administration of ^{14}C -GCA

Group	No. of Patients	(% dose/mmole $\text{CO}_2 \times \text{Kg}$ (Mean $\pm$ S.E.M.))				
		At 2 hours	At 4 hours	At 6 hours	At 8 hours	At 10 hours
Preoperative	26	0.01×0.004	0.03×0.004	0.10×0.01	0.12×0.01	0.13×0.08
Immediate Post-operative (IV Keflin)	5	Trace	Trace	Trace	Trace	Trace
8 to 10 days post-operative	11	0.51×0.12	0.59×0.10	0.40×0.04	0.24×0.02	0.04×0.02
5 to 12 months post-operative	20	0.24×0.04	0.37×0.05	0.35×0.04	0.27×0.04	0.06×0.04

FIG. 2. $^{14}\text{CO}_2$ excretion in the breath after the administration of ^{14}C -GCA.



the early $^{14}\text{CO}_2$ output, although it was less than in the early postoperative period. Figure 2 depicts the respiratory ^{14}C excretion in a diagrammatic form. During the first 6 hours there was an approximately 20 fold increase in CO_2 production in the early postoperative group and a 10 fold increase in the late postoperative group. During the 8-24 hour period the differences in CO_2 excretion between the various groups were not significant.

In Table 2 the $^{14}\text{CO}_2$ respiratory excretion is expressed as the cumulative percentage of the administered dose. The mean ^{14}C respiratory loss during the first 6 hours in the preoperative group was 2.2%, in the 8 to 10 day postoperative group it was 25.4%, and in the 5 to 12 month postoperative group it was 15.9%. In both postoperative groups the per cent loss was significantly increased ($p < 0.0005$) from the preoperative group. There was also a statistically significant difference between the two postoperative groups ($p < 0.05$); the ^{14}C excretion being higher in the early postoperative group.

The mean fecal excretion of ^{14}C is shown in Table 3. Preoperatively this was 6.6% of the given dose; in the early postoperative period this increased to 50.9% (p

< 0.0005), indicating very little bile salt absorption. In the late postoperative period the mean fecal ^{14}C excretion was 21.2%, indicating a significant ($p < 0.025$) compensatory increase in absorption.

Discussion

The combined measurement of expired $^{14}\text{CO}_2$ and fecal ^{14}C after the oral ingestion of ^{14}C -GCA provides a very sensitive measure of the fate of intraluminal conjugated bile acids. Bile acids are linked by an amide bond to either glycine or taurine and this bond is broken only by the action of bacterial enzymes.^{7,12} In normal subjects practically all the ^{14}C -GCA enters the enterohepatic circulation of bile salts via the terminal ileum, with only small amounts excreted as fecal ^{14}C -GCA, flatus $^{14}\text{CO}_2$, and breath $^{14}\text{CO}_2$ (Fig. 3). Normally less than 5% of the pool is lost each cycle into the colon, where bacterial deconjugation of the ^{14}C -GCA to free ^{14}C -glycine and cholic acid takes place. The ^{14}C -glycine is then rapidly absorbed by nonionic diffusion,^{2,17} enters the body glycine pool and is metabolized to $^{14}\text{CO}_2$ by tissue enzymes. The $^{14}\text{CO}_2$ is then carried via the bloodstream to

TABLE 2. Cumulative Specific Activities of Expired $^{14}\text{CO}_2$ (% of administered dose)

Group	No. of Patients	Cumulative excretion of $^{14}\text{CO}_2$ in breath (Mean $\pm$ S.E.M.)					0-24 hours
		0-2 hours	2-4 hours	4-6 hours	6-8 hours	8-24 hours	
Preoperative	26	0.30×0.36	0.50×0.39	1.44×0.95	2.29×1.65	20.09×9.06	24.62×2.20
8 to 10 days postoperative	11	8.33×6.80	8.97×6.19	8.09×4.44	5.29×2.26	18.51×6.15	49.19×5.74
5 to 12 months postoperative	20	4.36×3.07	5.41×3.09	6.15×3.10	5.24×3.22	23.05×13.60	44.21×5.10

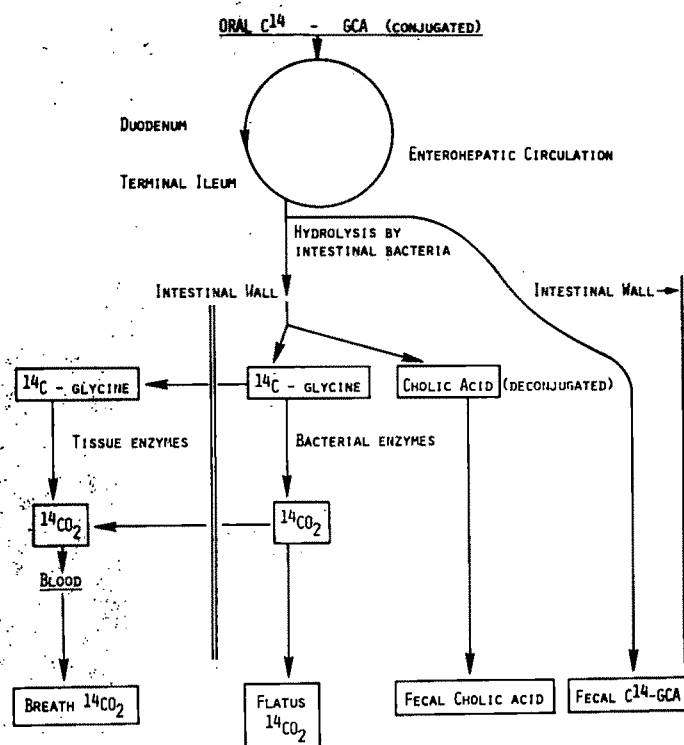
TABLE 3. Fecal ^{14}C Recovery and Weight of Feces*

Group	No. of Patients	^{14}C Recovery† Mean $\pm$ S.E.M.	Weight of Feces (gm/48 hours) Mean $\pm$ S.E.M.
Preoperative Control Period	20	6.6 $\pm$ 1.5	318 $\pm$ 42
Early Postoperative Period (4 to 10 days)	6	50.9 $\pm$ 11.9	1068 $\pm$ 287
Late Postoperative Period (5 to 12 months)	14	21.2 $\pm$ 7.2	897 $\pm$ 189

*Specimens of feces were collected for 48 hours following the oral administration of ^{14}C -GCA.

†Results are expressed as the percentage of the orally administered ^{14}C .

the lungs and excreted in the breath. Alternatively, bacteria in the intestinal lumen may cause glycine decarboxylation⁶ with the release of $^{14}\text{CO}_2$, which then rapidly diffuses through the intestinal wall of both the small¹¹ or large¹³ intestine. A small amount may be excreted as flatus $^{14}\text{CO}_2$. The major pathway for breath $^{14}\text{CO}_2$ is, therefore, by the liberation of glycine moiety, and its conversion to $^{14}\text{CO}_2$ by the intestinal bacterial enzymes,¹⁰ followed by the diffusion of $^{14}\text{CO}_2$ across the intestinal lumen and its transport via the bloodstream to the lungs. Some of the liberated glycine-1- ^{14}C , however, may be absorbed as such and converted to $^{14}\text{CO}_2$ by tissue enzymes.^{14,16} Therefore, the amount of $^{14}\text{CO}_2$ appearing in the breath is a direct reflection of the amount of bacterial deconjugation of the bile salts,¹⁸ whereas the fecal ^{14}C represents the amount of ^{14}C -GCA which is unabsorbed.

FIG. 3. The fate of oral ^{14}C -GCA.TABLE 4. Expected Results With the ^{14}C -GCA Breath Test

Status	Breath ^{14}C	Fecal ^{14}C
1. Normal Absorptive Ability and Normal Bacterial Activity.	Low	Low
2. Normal Absorptive Ability without Bacterial Activity.	Trace	Low
3. Bacterial Overgrowth.	High	Low
4. Malabsorption without Bacterial Activity.	Trace	High
5. Malabsorption and Normal Bacterial Activity.	High	High
6. Malabsorption with Adaptation and Bacterial Activity.	Intermediate	Intermediate

Consequently, the ^{14}C -GCA test may be useful to differentiate between the various causes of steatorrhea, since an increase in fecal ^{14}C is an indication of bile salt malabsorption, whereas an increase in breath ^{14}C is an indication of bile salt deconjugation (Table 4).

In the preoperative group both the breath and fecal ^{14}C were low, indicating that there was no malabsorption or intestinal bacterial decarboxylation of the bile salts. In the immediate 3 to 4 day postoperative period (with relative sterilization of the bowel), there was only a trace of ^{14}C in the breath, but the fecal ^{14}C content was highly elevated, indicating severe malabsorption without bacterial activity. In the 8 to 10 day postoperative period both the breath and fecal ^{14}C content were highly elevated indicating significant malabsorption and normal bacterial activity. Five to 8 months postoperatively both the breath and fecal ^{14}C content showed only a moderate elevation, indicating intestinal adaptation.

These data suggest that the ^{14}C -GCA test may be used to follow the adaptive response following bypass surgery for obesity. It may also be of help in the evaluation of patients with unsatisfactory weight losses following bypass. A significant increase in the breath and fecal ^{14}C soon after surgery, followed by a rapid decrease suggest an adequate bypass but an unusually fast adaptation. If the increase in the breath and fecal ^{14}C soon after the bypass is only moderate, then an inadequate bypass is suggested.

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Evaluation of the Nissen Fundoplication for Treatment of Hiatal Hernia:

Use of Parietal Cell Vagotomy Without Drainage as an Adjunctive Procedure

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Twenty-nine patients who underwent Nissen fundoplication for the treatment of symptomatic, sliding, esophageal hiatal hernia are reported. Fourteen of these patients also underwent parietal cell vagotomy (PCV) without a drainage procedure. Simultaneous cineradiography and manometric studies, esophagoscopy and gastric analysis were performed pre- and postoperatively. Esophageal acid clearing and pH reflux studies were performed postoperatively. All but 3 patients had reflux and/or esophagitis preoperatively. Cineradiography and the pH reflux test were the most reliable tests for diagnosis of reflux. There was no operative mortality. The mean followup period was 20 months. Dysphagia occurred in 5 patients. Correction of dysphagia in one patient required reoperation. The dysphagia in the remaining patients was temporary and mild, responding to dilatation. Two patients had mild diarrhea. One patient who had had a previous gastric resection developed severe diarrhea after bilateral truncal vagotomy. No patient developed the "bloat syndrome." A close correlation did not exist between reflux and preoperative sphincter pressure. The mean LES pressure increased 10 mmH₂O postoperatively and the two patients with persistent reflux postoperatively had normal LES pressure. Correction of reflux after Nissen fundoplication is probably due to some mechanism other than increased LES pressure. Recurrent or persistent hiatal hernia was diagnosed in 4 patients by cineradiography. Two of these patients had reflux but only the patient who had undergone PCV was without symptoms or esophagitis. The technical performance of the Nissen hiatal hernia repair was greatly facilitated by PCV. This procedure also provided adequate treatment for patients with concomitant duodenal ulcer disease. PCV, unaccompanied by a drainage procedure, was not associated with increased morbidity, mortality or the adverse effects usually attributed to vagotomy. In the event of recurrent hernia and reflux, PCV may prevent the development of esophagitis.

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IN 1951 Allison¹ indicated that the objective of hiatal hernia repair should be the prevention of reflux. The operation he recommended at that time, approximation of the crura and attachment of the phrenoesophageal ligament to the underside of the diaphragm, continued as the popular procedure for the next two decades. Allison,² on the basis of rigid radiological criteria, reported a recurrence rate of 49 per cent although symptoms were completely relieved or improved in 85 per cent of patients.

Earlier, disappointed with the high recurrence rate of the Allison repair, Nissen introduced the fundoplication principle for treatment of sliding hiatal hernia. The concept of fundoplication, *i.e.*, wrapping the lower end of the esophagus with the walls of the stomach, has been used also by Belsey¹⁴ and incorporated into the posterior gastropexy of Hill.¹⁵ The clinical success rate of the various procedures has been reported as 93 per cent for the Nissen,³⁶ 85 per cent for the Belsey³⁰ and 96 per cent for the Hill.^{15,32}

Opinions vary as to the desirability of adding vagotomy and drainage as an adjunctive procedure to hiatal hernia repair. The most prevalent opinion suggests that vagotomy is unnecessary if the hernia repair is adequately done and no duodenal ulcer is present.²⁸ This paper reports our results with the Nissen fundoplication operation in 29 patients. It was noted in those patients who had

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a coexistent duodenal ulcer that vagotomy helped to isolate the esophagogastric junction, making it possible to perform the fundoplication procedure with greater anatomical precision. This observation, in conjunction with the absence of dumping and diarrhea after parietal cell vagotomy (PCV) without drainage performed for treatment of duodenal ulcer,¹⁹ led us to combine the latter procedure with the Nissen fundoplication in our last 14 patients even when a duodenal ulcer was not present.

Methods

Twenty-nine patients, including 27 males and two females, were studied. The mean age was 49 years (range 23-69). The patients were divided into three groups. Group I: 11 patients underwent Nissen fundoplication alone. Group II: 4 patients underwent conventional vagotomy and a drainage procedure as well as the Nissen procedure. Group III: 14 patients had Nissen fundoplication combined with PCV. Eight of the 29 patients had or had had active duodenal ulcer disease in addition to a symptomatic hiatal hernia. Three patients had been operated upon elsewhere for hiatal hernia, one patient having undergone surgery twice.

The preoperative evaluation of all patients included measurement of basal and maximal acid gastric secretory rates, an upper gastrointestinal roentgenographic study, esophagoscopy, esophageal biopsy in those patients without gross evidence of esophagitis, measurement of sphincter pressure, and motility studies made simultaneously with cine roentgenograms. Surgery was performed for intractable symptoms of esophagitis, dysphagia unrelated to a primary motor disorder, reflux resulting in aspiration and complications of obstruction or bleeding. Reflux and/or esophagitis was present in all but 3 patients. Ten patients had normal LES pressure, yet all but one of these had reflux and/or esophagitis. Postoperatively, patients were evaluated clinically and the preoperative studies were repeated. In addition, tests to measure the clearing of acid from the esophagus and to measure the reflux of acid from the stomach into the esophagus were carried out on 20 patients. Most patients were studied after operation just prior to discharge and one or more times several months or years later.

Motility and Pressure Studies

The technique for performing simultaneous manometric measurements and cineradiography was described previously.¹⁷ Manometric measurements were made using three 5 X 7 mm radiopaque transducers, calibrated in cm H₂O at 38°C. They were passed down the esophagus attached to long, fine, flexible wires that were connected to a preamplifier and a recording galvanometer. There was a distance of 5 cm between the distal and middle transducers and 10 cm between middle and proximal transducers. A glass pH electrode was located at the

middle transducer. This was connected to a pH meter for continuous recording.

The bundle of monitors also included two small polyethylene tubes. The opening of one was located at the distal transducer and used to instill acid into the stomach in the acid reflux test. The opening of the other was at the proximal transducer for the purpose of placing acid into the esophagus in the acid clearing test.

The bundle of tubes and monitors was swallowed by the patient until the transducers were in the stomach. The bundle was pulled through the gastroesophageal junction in 0.5 cm increments until the two proximal transducers were positioned in the esophagus and the distal transducer positioned at the gastroesophageal junction. Lower esophageal sphincter (LES) pressure greater than 12 cm H₂O above fundic pressure was considered normal.

Acid Clearing Test

With the bundle remaining in the position reached at the conclusion of the pull through, 15 cc of 0.1 N HCl were instilled through the proximally placed catheter (15 cm above the high pressure zone (HPZ) and 10 cm above the pH electrode). The patient was instructed to swallow at 30 second intervals and the pH was noted before each successive swallow. The number of swallows required to raise the pH to 5.0 was recorded. The test was considered abnormal when more than 12 swallows were necessary.

pH Reflux Test

The two distal transducers were returned to the stomach, and 200 ml 0.1 N HCl was instilled through the distal catheter into the stomach. The catheter was flushed with saline solution and the bundle withdrawn so that the middle transducer and pH electrode were located 5 cm above the HPZ. If the esophageal pH was low, saline was instilled through the proximal catheter to clear the esophagus of acid. Before commencing the test, it was necessary that the pH of the mucosa remain stable and above 5.0.

The patient was asked to breathe deeply, to cough and to strain in sequence. Each maneuver was performed in the supine, right lateral decubitus, left lateral decubitus, and Trendelenburg position. The pH of esophageal mucosa was recorded after each maneuver and in each position. If the pH dropped below 5.0 after any maneuver, a pause was made to allow the pH to return to neutral before continuing. Results were interpreted according to Skinner's²¹ classification. Failure of the pH to fall at any time during the test meant no reflux. A transient drop of the pH below 4.0 with one or two of the maneuvers was interpreted as 1+ reflux. Reflux was considered 2+ or 3+ if the pH fell below 4.0 with more than 2 or 8 of the maneuvers respectively.

TABLE 1. *Length of Followup*

Operation	1-6 mon.	7-12 mon.	1-2 yrs.	2-3 yrs	>3 years
Nissen			1	6	4
Nissen and Vagotomy			2	2	
Nissen and Parietal Cell Vagotomy	9	2	2	1	
Total	9	2	5	9	4

Gastric Analysis

The basal gastric secretory rate was determined for two hours. This was followed by a two hour collection period after stimulation with Histalog. Two to 34 months postoperatively a Histalog test was repeated and an insulin test was performed on patients who had undergone vagotomy. A preoperative response to Histalog was elevated if it exceeded the value obtained from a control group of similarly aged patients. The insulin test was interpreted according to the criteria of Hollander.¹⁶

Results

Clinical

Nine of the 29 patients were followed for one to 36 months and were asymptomatic when last seen. Cineradiography was performed on 6, motility studies on 2, and esophagoscopy on one patient. These studies were all normal. One patient was asymptomatic 5 years postoperatively but cineradiography and motility studies performed two weeks after operation were the only objective data obtained. The remaining 20 patients were studied in detail both pre- and postoperatively and form the basis for this report. The mean followup period for all patients was 20 months (Table 1).

There was no operative mortality. Three patients required postoperative dilatation for dysphagia. These patients did not have a bougie in the esophagus when the fundoplication was performed. Two of these patients also had had conventional vagotomy. Dysphagia was of such severity in one of the latter patients that after 4 months the original procedure was taken down and the stomach again wrapped around the esophagus while a 40 Fr. bougie was in the esophagus. Disappearance of dysphagia after the second operation emphasizes the importance of this maneuver. In the second patient with dys-

TABLE 2. *Evaluation of Results by Patients*

Operation	Number Patients	Excellent	Good	Fair
Nissen	11	10	0	1
Nissen and other Vagotomy	4	1	2	1
Nissen and PCV	14	12	2	0
Total	29	23	4	2

phagia after vagotomy, it was concluded on the basis of motility studies that he had had diffuse esophageal spasm which had been unrecognized preoperatively. He responded satisfactorily to dilatation and required no further surgery. Two additional patients in whom a bougie was used at operation had mild to moderate dysphagia following hernia repair and PCV. One of these patients had severe transmural esophagitis and shortening of the esophagus. The esophagus was perforated in the dissection and the plication used to patch the esophagus was left in the chest.

Diarrhea occurred in three patients after vagotomy. The diarrhea was mild, intermittent, and of no concern to the two patients with PCV. A third patient who had had antrectomy and a Billroth I anastomosis performed previously, developed severe and persistent diarrhea (10 to 15 bowel movements without medication) which was attributed to bilateral truncal vagotomy performed at the time of his hiatal herniorrhaphy.

After Nissen hiatal herniorrhaphy and PCV, one patient complained of vomiting and postprandial epigastric pain incited only by the ingestion of milk. He had radiological evidence of a small recurrent hernia and reflux. Endoscopically he had no esophagitis. Another patient complained of postprandial epigastric and substernal discomfort two years following a Nissen repair. He had a recurrent hernia and esophageal reflux demonstrated radiologically, and moderate esophagitis observed on esophagoscopy.

The patients' evaluations of their clinical results are tabulated in Table 2. Of the 20 patients fully studied, 15 had an excellent result, 4 patients had a good result, and one had only a fair result. Six patients in the excellent category had some symptom in the early postoperative period that disappeared; or they had mild, intermittent diarrhea or abdominal discomfort which was easily controlled and well tolerated. One patient required a revision of the herniorrhaphy before being placed in the excellent category. The one patient with a fair result had had only a Nissen procedure. He continued to have substernal burning pain made worse on reclining. He was improved by the operation and wanted no further surgery. Of the remaining 9 patients who would not submit to postopera-

TABLE 3. *Mean Lower Esophageal Sphincter Pressures*

Operation	Cm. of Water Above Fundic Pressure		
	Preop.	<2 mon. Postop.	>2 mon. Postop.
Nissen	12.1 ± 9	20.5 ± 8	24.5 ± 8
Nissen and other Vagotomy		26.7 ± 10	16.8 ± 6
Nissen and PCV		19.8 ± 6	20.7 ± 5
Mean LES Pressure		21.4 ± 10	22.2 ± 9

±Standard deviation

TABLE 4. Summary of Patients with Recurrent Hernia

Case	Operation	Months of followup	Recurrence (Cine)	Reflux (Cine)	Reflux (pH test)	Esophagitis	Symptoms of reflux
1	Nissen	26	+	-	-	-	-
2	Nissen	28	+	+	+	+	+
3	Nissen	41	+	-	-	-	-
4	Nissen and PCV	10	+	+	+	-	-

tive testing, 8 had excellent and one had fair results. Therefore, 27 of 29 patients, (93 per cent) had excellent or good clinical results.

Manometric Studies

The mean LES pressure preoperatively was $12.1 \pm \text{SD } 9$ cm H₂O above fundic pressure. Fifteen patients had LES pressure below this level. The mean pressure in the early postoperative period was $21.4 \pm \text{SD } 10$ cm H₂O and in those studies performed longer than 2 months after operation the mean pressure was $22.2 \pm \text{SD } 9$ cm H₂O (Table 3).

Cineradiographic Studies

Cineradiographic studies were conducted simultaneously with manometric studies in 27 preoperative and 25 postoperative patients. Frequently more than one study was done postoperatively. Reflux was demonstrated in 22 patients preoperatively. Postoperatively, 4 patients had evidence of recurrent hiatal hernia, 2 of these patients demonstrated reflux, one of which was symptomatic. Diffuse spasm was suspected on the basis of cineradiography in two patients and confirmed manometrically in one. No patient had postoperative evidence of stricture.

Gastric Analysis

All patients had gastric analysis performed preoperatively. Sixteen patients secreted gastric juice in excess of the normal controls. Thirteen of the 18 patients who had vagotomy were retested postoperatively. Complete vagotomy as judged by the Hollander test¹⁶ occurred in 9 of the 11 patients who had PCV and in both patients who had conventional vagotomy. The patients who had complete vagotomy had a decrease in their secretory response to Histalog of 72.6 per cent $\pm \text{SD } 20$.

Endoscopy

Preoperatively, esophagitis was present in 22 of 28 patients esophagoscoped. Esophagitis was present in 13 of the 16 patients who had acid secretion in excess of the control patients and in all patients who had both hyperse-

cretion and radiological evidence of reflux. The incidence of esophagitis was almost identical in patients with gastric acid hypersecretion (13 of 16 or 81%) as in those with normal acid values (9 of 12 or 75%). The incidence of esophagitis was unrelated to LES pressure but did occur with greater (19 of 20 or 95%) frequency in patients in whom reflux was demonstrated by cineradiography than in those patients in whom reflux was not demonstrated (3 of 7 or 43%) by this means. Of the 18 patients esophagoscoped pre- and postoperatively, esophagitis was present in 16 preoperatively and in 3 postoperatively although it was less severe in these patients than it had been preoperatively.

Acid Clearing Test

This test was performed on 20 patients after operation and was normal in 6 and abnormal in 14. There was no relation between the results of the acid clearing test and the patient's postoperative symptoms, presence of esophagitis, or reflux. The large number of false positive acid clearing tests suggests that this test has little to recommend it in postoperative testing. The test may have its greatest value in the detection of esophagitis preoperatively.

pH Reflux Test

Valid studies were performed in 18 of 20 patients tested. The test was negative in 16, 1+ in one, and 2+ in one patient. The one patient with a 2+ positive test had esophagitis; symptoms of reflux and reflux demonstrated by cineradiography. The patient who was 1+ positive had minimal reflux demonstrated by cineradiography, had no esophagitis by biopsy, had a very small recurrent hernia and no symptoms of reflux.

Recurrent Esophageal Hiatal Hernia

Based on the cineradiographic studies performed on 25 of the 29 patients, persistent or recurrent hiatal hernia occurred in 4 patients and the results reported in Table 4. Only one of the 4 patients had symptoms of reflux. At 26 months postoperatively, this patient had moderate esophagitis on esophagoscopy which was confirmed by biopsy. Diffuse inflammation of the entire gastric and

duodenal mucosa was present. The lower esophageal sphincter was incompetent and reflux was present. The LES pressure had decreased from 22.8 cm H₂O two weeks postoperatively to 13.5 cm H₂O. A persistent hiatal hernia was confirmed by cineradiography. The patient was a hypersecretor and had not had a vagotomy. He declined further surgery.

Discussion

The results presented indicate that for prevention of reflux, Nissen's fundoplication operation accomplished this primary objective effectively. Indeed, Nissen²⁶ suggested that a hiatal hernia should be regarded as the result, rather than the cause of reflux and that reduction of the hernia in the classical sense was no longer the goal of therapy. In support of this concept, Hiebert and Belsey¹⁴ observed that, in 71 patients with incompetency of the cardia but without radiological evidence of hiatal hernia, the patient's average age was 15 years less than the average age in patients with hiatal hernia. They concluded that incompetency of the esophagogastric junction might be the precursor of hiatal hernia.

Fifty-six per cent of our patients who were symptomatic with their hiatal hernia had acid hypersecretion; while other authors^{13,35} have observed hypersecretion in almost all patients with esophagitis. Esophagitis was present in 81 per cent of our patients with so-called "hypersecretion" and in 75 per cent of the "normal secretors." These observations suggest that while reflux of acid is important in the production of esophagitis, the concentration of acid need not be excessive nor does hypersecretion of acid ensure the development of esophagitis. The sensitivity of esophageal mucosa to the corrosive action of gastric juice must vary. Thus vagotomy as a part of the hernia repair is warranted if it can be done without morbidity, for reduction of acid secretion below the threshold required to produce esophagitis in a given individual may prevent this complication if reflux recurs.

Manometric studies of the esophagus are important in the evaluation of patients with hiatal hernia in whom repair is contemplated, for it is by this means that motor disorders, unsuspected and unrelated to the hiatus hernia, can be detected. It is important to recognize such patients before a hiatal herniorrhaphy is inappropriately performed for the results of hiatal herniorrhaphy are likely to be unsatisfactory if the existence of a significant motility disturbance is unrecognized. This was emphasized by Bombeck⁶ who described 5 patients with diffuse esophageal spasm in whom preoperative symptoms persisted despite the healing of esophagitis following a successful Nissen fundoplication. One of our patients who had unrecognized diffuse spasm also continued to have symptoms after successful hernia repair.

There is controversy regarding the importance of the LES pressure in the prevention of reflux and the as-

sociated clinical symptoms. We noted, as did Winans,³⁴ that LES pressure varied significantly in the same individual if measurements were repeated over several months. We observed an increase in the LES pressure postoperatively in most patients but there were 4 patients who had an abnormally low pressure either in the early or late postoperative studies. None of these 4 patients had symptoms of reflux. After fundoplication, significant increases in LES pressure were observed by Battle⁴ as well as others while Moran²³ noted an increase in the LES pressure of 9 patients and a slight decrease in 7 successfully treated patients. Clinical improvement therefore does not necessarily depend on an increase in the LES pressure. Battle,⁴ for example, noted no increase in the LES strength following successful medical therapy. We agree with Moran²³ that augmentation of LES pressure by surgery is desirable but may be of secondary importance in the prevention of reflux in a successfully treated patient.

Haddad¹² reported that reflux determined by pH was consistently related to a low sphincter pressure. The presence of normal or increased sphincter pressure preoperatively in nine of our patients who had esophagitis and cineradiographic evidence of reflux failed to support this finding. Likewise, normal sphincter pressure in the two patients with a positive pH reflux test postoperatively demonstrated that decreased LES pressure was not essential for the occurrence of reflux.

Postoperatively we looked for reflux by cineradiography and by pH measurement. Determination of reflux by pH measurements after the method of Tuttle and Grossman³³ is known to yield a substantial number of false positive results. We, therefore, adopted the method of Skinner and Booth.³¹ Two out of 18 patients studied postoperatively had a positive reflux test. Both of these patients had cineradiographic evidence of reflux and recurrent hiatus hernia. The patient who was achlorhydric after PCV had no esophagitis and was clinically satisfactory. The other patient who had not undergone vagotomy had a high gastric secretory rate and persistent esophagitis.

The incidence of recurrent herniation following the Nissen fundoplication varies in different reports depending on the period of followup, the number of patients studied and the criteria used for recurrence. Krupp and Rossetti²⁰ reported 4 recurrences in 109 patients; Casten⁹ had a 10 per cent recurrence rate among 88 patients who also had vagotomy and pyloroplasty; Polk and Zeppa²⁹ reported 4 per cent anatomical and physiologic failures two and one-half years postoperatively (international survey); Woodward's³⁶ radiographic recurrence rate was 5 per cent and when vagotomy and pyloroplasty were added, it was 7 per cent. Ellis¹¹ reported radiological evidence of recurrent herniation and reflux in one of 22 patients with uncomplicated hiatal hernia. Moran²³ re-

ported one recurrent hernia in 40 patients. In our series of 29 patients, there were 4 radiographic recurrences, only one of which was symptomatic and associated with esophagitis. In one patient who is asymptomatic and without reflux, the plication was intentionally left in the chest. This emphasizes the point that correction of reflux is more important than elimination of the hernia. Therefore, the radiographic evidence of a persistent hernia is not of great concern so long as reflux and esophagitis are not present.

Dysphagia and "gas-bloat syndrome" are regarded as specific complications of fundoplication. In Woodward's³⁶ experience the "gas-bloat syndrome" occurred in 54 per cent of patients undergoing a Nissen fundoplication alone and in 44 per cent of patients who had vagotomy and pyloroplasty in addition. Dysphagia was encountered by Woodward in 24 per cent of patients after fundoplication and 14 per cent when vagotomy and pyloroplasty were added. Because of these results Woodward suggested restricting the Nissen fundoplication to those patients with failure of previous hiatal herniorrhaphy and to those with peptic strictures of the esophagus.

Although our number of patients is small we have not encountered the "gas-bloat syndrome" and dysphagia has not been a problem. The fear that these two complications might occur does not cause us to restrict the use of this procedure. Although dysphagia is known to occur following vagotomy,¹⁸ the dysphagia that we encountered after Nissen fundoplication was attributed to the presence of an unrecognized esophageal motility disturbance, or to the failure to use an esophageal bougie as a guide at operation to prevent excessive constriction of the esophagus.

Increased gastric acid secretion in patients with hiatal hernia has been reported^{8,13,35} and Winkelstein¹⁹ and Herrington¹³ have specifically emphasized the relationship between acid hypersecretion and esophagitis. The number of patients with hiatal hernia who also have duodenal or gastric ulcer has ranged from 10 to 79 per cent.^{3,7,21,27,28} In this connection, the presence of fundic mucosa in the duodenum of 10 per cent of patients with reflux esophagitis was an interesting observation by Paulino.²⁷ Eight of our patients (27%) had or had had concomitant duodenal ulcer and hiatal hernia.

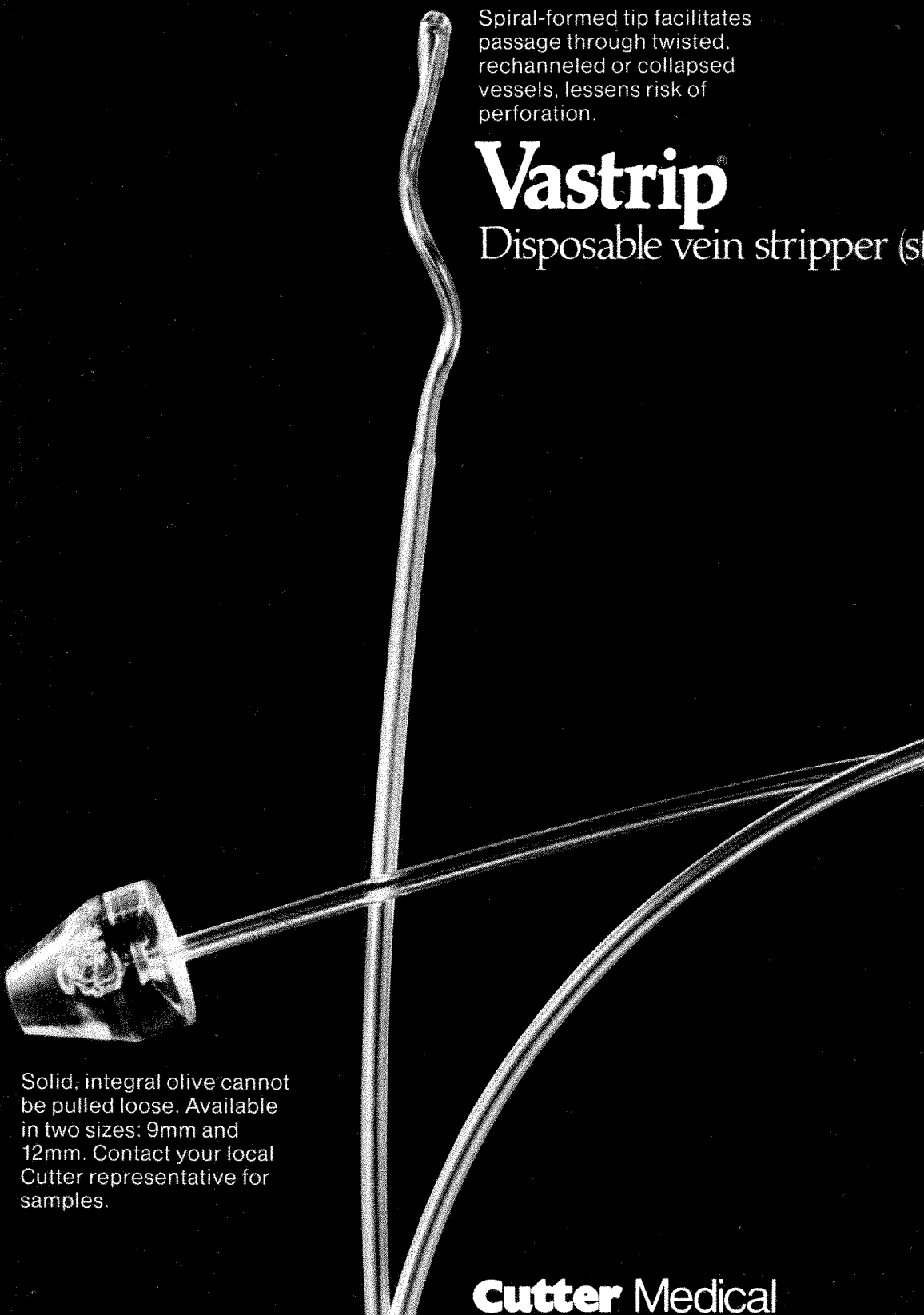
Berman⁵ in 1961 spoke of the "hiatal hernia syndrome" and advocated a "balanced operation" that consisted of reduction of the hernia, repair of the esophageal hiatus, restoration of the angle of His, vagotomy and pyloroplasty and correction of any associated lesion. For a while this concept was popular.^{9,10,13} Subsequently truncal vagotomy and drainage as ancillary procedures fell into disfavor in the surgical treatment of hiatus hernia because of the adverse symptoms related to dumping and post vagotomy diarrhea.^{9,10,13,24,28,32}

Since PCV without an accompanying drainage procedure is associated with nearly normal gastric emptying, only occasional mild dumping and infrequent mild diarrhea and because the abdominal vagi do not have an important role in maintaining human gastroesophageal sphincter pressure,²² it seemed reasonable to presume that PCV without drainage as an adjuvant surgical procedure at the time of hiatal hernia repair might provide the advantages of vagotomy noted by Pearson²⁸ without the disadvantages that occur with pyloroplasty and truncal vagotomy. The occurrence of one recurrent but asymptomatic hernia in 14 patients who underwent the procedure supports this conclusion. The mobilization of the lesser curvature of the stomach, required to perform PCV, has the additional advantage that the fundoplication can be accomplished with more ease and with greater anatomical precision. The effectiveness of the plication may be improved by this technique.

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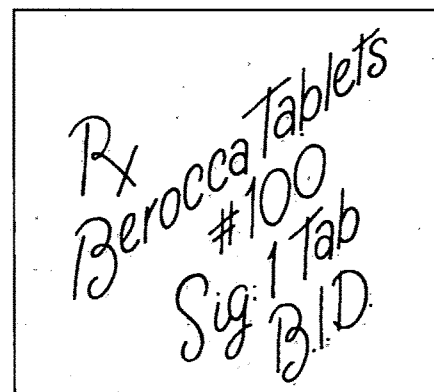
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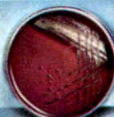
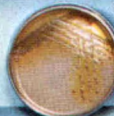
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 <i>Proteus</i> species, indole-negative	97%	99%	98%	98%
 <i>Proteus</i> species, indole-positive	98%	96%	96%	96%
 <i>Pseudomonas</i> <i>aeruginosa</i>	95%	95%	94%	94%
 <i>Klebsiella-Enterobacter- Serratia</i>	97%	98%	98%	98%
Staphylococcal Susceptibility No. of patient tests	96% 1,550*	94% 1,631*	97% 2,941**	96% 3,268**
 <i>Staphylococcus</i> <i>aureus</i>	96%	95%	97%	97%
 <i>Staphylococcus</i> , all others	96%	92%	97%	94%

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Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, *Proteus* species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported. **Note:** The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSE AND ADMINISTRATION

GARAMYCIN Injectable may be given

intramuscularly or intravenously.

For Intramuscular Administration: Patients with normal renal function*

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lbs.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

*In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

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AHFS Category 8:12.28

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Garamycin®

gentamicin
sulfate

Injectable

40mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

Urea Production Related to Intraperitoneal Inflammation

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To elucidate a possible connection between the amount of urea production and degree of intraperitoneal complication 24 hour urea production was studied in patients having undergone appendectomy. The base material consisting of 60 patients with an uncomplicated postoperative course was divided into three groups: 1) 20 patients with a normal appendix without any infection, 2) 20 patients with acute appendicitis without perforation, and 3) 20 patients with acute appendicitis with perforation and varying degrees of peritonitis. Twenty-four hour urea production was determined from the second to seventh postoperative day. A significant difference in postoperative urea production was found between the three groups mentioned, the patients in group 3 had the highest and the patients in group 1 the lowest urea production. Further, all three groups showed a gradual, significant decrease in urea production from second to seventh postoperative day. Two patients with intraperitoneal complications after appendectomy had a significantly increased urea production.

THE IMPORTANT DIAGNOSIS of intra-abdominal inflammatory complications to surgery can in some cases be difficult even if careful clinical examination is supplied by expert radiological service. Help can be gained through ultrasonic scanning and scintigraphy using radioactive labelled leucocytes, and determination of serum catecholamines has also been proposed.²⁻⁴

Experiences concerning the intensity of urea production as an aid to the diagnosis of postoperative intra-abdominal complications in patients with acute renal failure have been published previously.⁵ This simple and inexpensive method of examination has proven valuable in several other patients by showing a very high urea production when intra-abdominal abscess was present and decrease in urea production following sufficient drainage. This communication reports further studies on the relationship between urea production and intra-abdominal inflammation.

Materials and Methods

Patients undergoing appendectomy were chosen for the study. These are naturally grouped into three

categories: 1) patients who were operated on for suspicion of appendicitis but had a normal appendix removed. At laparotomy no abdominal or pelvic inflammatory lesion was registered, 2) those in whom the appendix was inflamed but not perforated, and 3) those with perforation. Each group comprised 20 consecutively operated patients with a smooth recovery. Pregnancy, age below 14 years and concomitant inflammatory diseases led to exclusion. Two patients were excluded because of postoperative intraperitoneal complications.

Fourteen women and 6 men (mean age 25 years, mean weight 65 kg) had a normal appendix. Both appendicitis groups comprised 7 women and 13 men. Those without perforation had a mean age of 27 years and a mean weight of 65 kg, and corresponding values for perforated cases were 38 years and 65 kg.

All patients had the same postoperative treatment and a normal diet was gradually resumed, beginning with fluids. Urea production was evaluated on the second to seventh postoperative day by daily determination of diuresis and urea concentration in the urine. Serum urea concentration was also measured daily.

Results

The daily urea production in the three groups is given in Table 1. The postoperative urea production was lowest when a normal appendix had been removed and highest when the inflamed appendix had perforated. By using an analysis of variance a significant difference was found between the three groups. ($F = 48.9$, critical F value 5% = 3). Furthermore an even decrease in urea production was observed during the postoperative period in each group, and a significant negative regression was found. The regression lines are not identical but localized on separate levels (Fig. 1).

As already mentioned two patients developed post-

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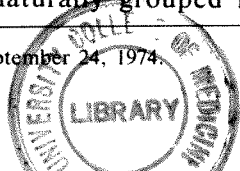


TABLE 1. Postoperative Production of Urea, g/24 hr, (mean $\pm$ SD), After Appendectomy. Each Group has 20 Consecutive Patients.

Postop day	Normal appendix	Acute appendicitis	Appendicitis and Perforation
2	17.65 $\pm$ 4.87	21.89 $\pm$ 5.88	28.43 $\pm$ 9.21
3	17.15 $\pm$ 6.11	21.17 $\pm$ 5.55	29.24 $\pm$ 9.30
4	16.11 $\pm$ 4.98	19.26 $\pm$ 5.81	23.75 $\pm$ 8.75
5	15.93 $\pm$ 5.59	19.93 $\pm$ 7.05	24.57 $\pm$ 10.23
6	13.40 $\pm$ 5.62	20.19 $\pm$ 6.41	24.91 $\pm$ 12.75
7	12.88 $\pm$ 4.78	17.64 $\pm$ 5.54	22.78 $\pm$ 10.44

operative complications following appendectomy. In both cases the urea production was significantly raised (Figs. 2 and 3).

Discussion

In a previous study we demonstrated that in patients with postoperative acute anuria, urea production increases when anuria is caused by an inflammatory intraperitoneal complication. In the present investigation an attempt has been made to elucidate a possible connection between the amount of urea production and degree of intraperitoneal inflammation.

The examination showed a significant difference in postoperative urea production between the three groups. Urea production was highest in patients with appendix inflammation, perforation, and varying degrees of peritonitis. In patients with appendix inflammation without perforation, urea production was found to be higher than in those who had a normal appendix removed.

Further, for all three groups, the investigation showed a progressive, significant fall in urea production from the second to seventh postoperative day.

Two patients with intraperitoneal complications after appendectomy had abnormal urea production curves. In one patient (Fig. 2) a marked rise in urea production occurred before recognition of intra-abdominal abscess, while in the other patient (Fig. 3) an increase in urea production did not occur until the patient displayed symptoms of intraperitoneal complication, and reoperation was performed. The significantly increased urea production after reoperation was probably due to the combination diffuse peritonitis, sepsis, and pneumonia.

Besides infections it is well known that traumata and large burns can cause increased urea production.⁶ Also variation in food intake can be the cause of variation in urea production, but usually only few grams per 24 hours,^{1,6} therefore it is reasonable to assume that this may be disregarded if urea production is used as a diagnostic parameter.

Determination of daily urea production is a simple and inexpensive examination method, and our observations

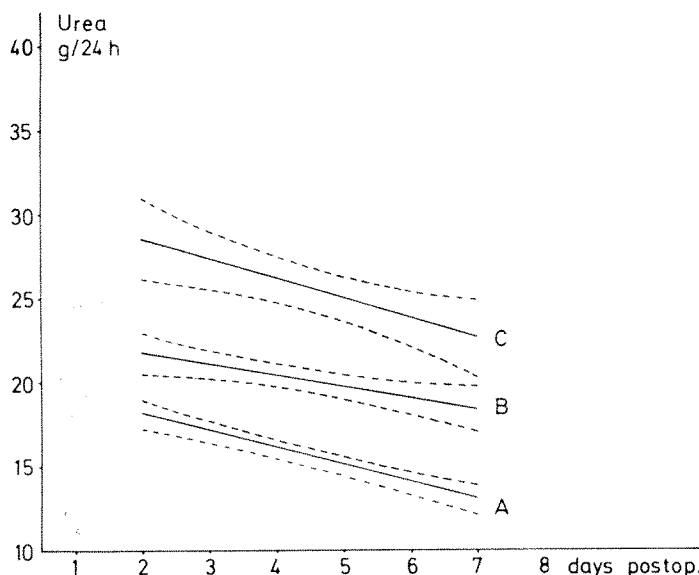


FIG. 1. Estimated regression lines and confidence limits for urea production after appendectomy. A: normal appendix. B: acute appendicitis. C: acute appendicitis and perforation. A: $y = 20.07 - 1.007 \cdot x$; $s_b = 0.148$; $t = 6.8$; $P < 0.001$. B: $y = 23.04 - 0.670 \cdot x$; $s_b = 0.211$; $t = 3.2$; $P < 0.002$. C: $y = 30.88 - 1.169 \cdot x$; $s_b = 0.567$; $t = 2.06$; $P < 0.05$.

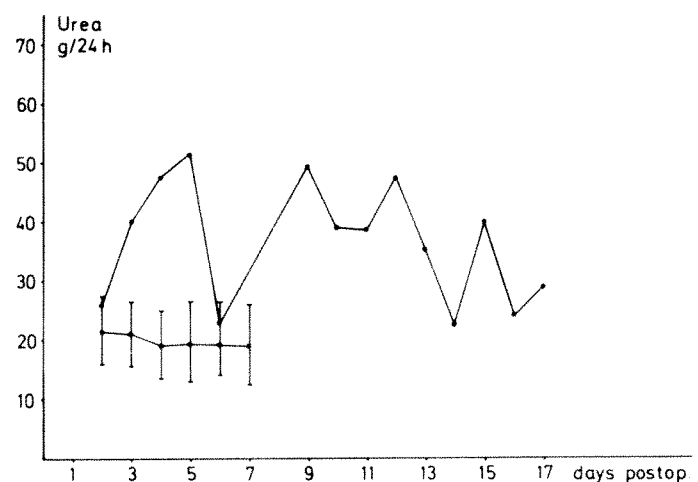


FIG. 2. Postoperative urea production curve in 19-year-old man with acute appendicitis with complication of the postoperative course by pelvic abscess and wound infection. The curve is compared with the urea production (mean $\pm$ SD) in 20 patients with uncomplicated postoperative course after appendectomy for acute appendicitis.

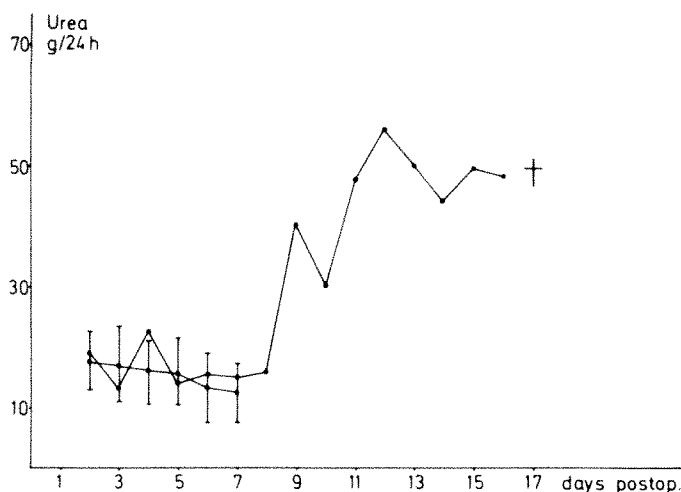


FIG. 3. Postoperative urea production curve in 19-year-old woman with normal appendix, but with complication of the postoperative course by diffuse peritonitis. The curve is compared with the urea production (mean $\pm$ SD) in 20 patients with uncomplicated postoperative course after appendectomy (normal appendix) on suspicion of appendicitis.

indicate that this method could be a simple aid to the diagnosis of abdominal inflammatory surgical complications. Increasing values in the days following surgery should arouse suspicion and very high values could support an uncertain clinical suspicion of intra-abdominal inflammation. Our observations can only point to this possibility, and further studies are needed.

Conclusion

The examination intends to elucidate a possible connection between the amount of 24 hour urea production and degree of intraperitoneal inflammation. The base material consists of 60 patients with an uncomplicated

postoperative course after appendectomy. The patients were divided into three groups: 1) 20 patients with a normal appendix without any infection, 2) 20 patients with acute appendicitis without perforation, and 3) 20 patients with acute appendicitis with perforation and varying degrees of peritonitis. Twenty-four hour urea production was determined from the second to seventh postoperative day. A significant difference in postoperative urea production was found between the three groups mentioned, the patients in group 3 had the highest and the patients in group 1 the lowest urea production. Further, all three groups showed a gradual, significant decrease in urea production from second to seventh postoperative day. Two patients with intraperitoneal complications after appendectomy had a significantly increased urea production. It was concluded that determination of 24 hour urea production is a simple and inexpensive method which may be of diagnostic value on clinical suspicion of intraperitoneal inflammatory complications.

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Twenty-four Hour Left Ventricular Bypass with a Centrifugal Blood Pump

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A new centrifugal blood pump system has been developed for left ventricular bypass by the addition of non-thrombogenic blood surface materials and an ultrathin-walled cannula for the retrograde cannulation of the left ventricle. Partial LV bypass at 3 to 6 L/min was undertaken in 55 calves without thoracotomy. In 20 it was continued for 24 hours, with 13 survivors who were eventually sacrificed. Eleven of the last 14 experiments were completed without mishap. Heparin was employed only during pump insertion. Hematologic changes were limited to moderate platelet depression, and tolerable hemolysis (average serum level 21 mg% in the last 13 experiments). Normal clotting parameters and the absence of significant fibrin split product formation correlated with the absence of gross thrombosis and few minor renal emboli observed at autopsy. This pump system appears to have several advantages over previously described equipment for LV bypass.

EFFORTS AT SUPPORTING the failing heart have resulted in an increasing use of circulatory assistance techniques, particularly for acute left ventricular pump failure, as seen in acute myocardial infarction and shock^{10,20,21} or after cardiopulmonary bypass.¹ Recent clinical experience with intra-aortic balloon counterpulsation suggests that it is effective in some of these patients, but is limited in dealing with severe degrees of pump failure.^{10,20,21} Left ventricular bypass has several theoretical advantages over intra-aortic balloon counterpulsation under such circumstances, including the production of a normal cardiac output, direct decompression of the left atrium and ventricle, and insensitivity to marked aberrations in cardiac rate and rhythm. For these reasons, the further development of left ventricular

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bypass systems for the temporary and permanent support of the failing heart appears justified.

This report details the results of animal trials of a new non-thoracotomy extracorporeal left ventricular bypass system, which has been designed for extrathoracic insertion, minimal anticoagulation requirements, low hemolysis, and high flow. Experimental trials of this system were performed in 55 calves in an effort to develop appropriate surgical implantation techniques, determine system reliability, and study animal tolerance and blood damage.

The system is based on a compact, centrifugal blood pump driven by electromagnetic coupling. Details of the design and performance of this pump have been reported previously.^{3,4,7,9} The pump is an open impeller centrifugal design capable of up to 8000 rpm (Figs. 1 and 2). It generates a pressure in proportion to its rotational speed, and the flow rate at any generated pressure is determined by the resistance of the perfused bed. Pump rotation is controlled by an externally rotating electromagnetic field, and is most efficient in the steady flow, or pulseless mode, which was employed in the present experiments. However, the pump may be pulsed in synchrony with an ECG-triggered signal, with a variable pulse delay, amplitude and wave form. Non-thoracotomy access to the left ventricle via the calf's common carotid artery was accomplished with a thin-walled (0.01 inch), flexible, non-kinking left ventricular cannula (Fig. 3). A non-thrombogenic urethane elastomer or LTI pyrolytic carbon were employed for all blood contact surfaces, and permitted the use of heparin to be limited to the period of cannula insertion.

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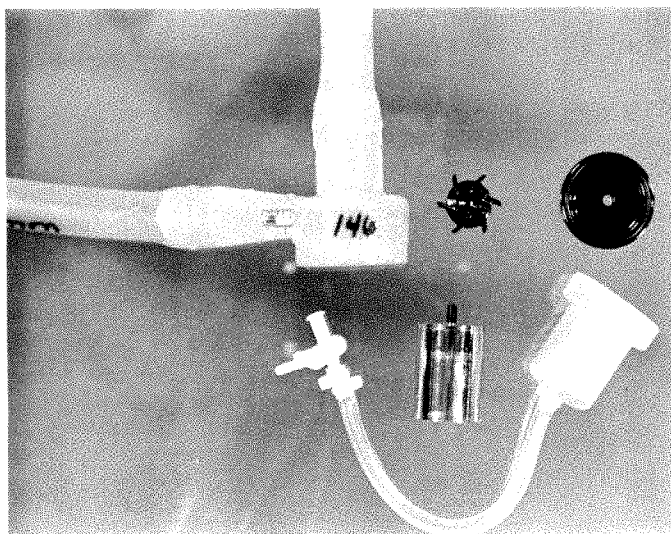


FIG. 1. Components of the centrifugal pump, which include pyrolytic carbon impeller and baffle, stainless steel rotor with implanted magnets, and outer pump scroll and cup. The impeller and rotor are joined to form the single moving part in the assembled system.

Methodology

A. Animal Implantation

Healthy calves weighing approximately 70 kg were fasted for 48 hours with the exception of water, premedicated with 4 mg atropine sulfate, and anesthetized with 4% Halothane and oxygen by mask. Surgery was limited to the neck, where catheters were implanted in the internal jugular vein for infusion and central venous pressure monitoring, and through the left external carotid artery into the aorta for central aortic pressure monitoring. In addition, a Swan-Ganz catheter was floated into the pulmonary artery for thermodilution cardiac output measurements. An antibiotic regimen was started just prior to pump implantation, to include aqueous penicillin, one million units, and Streptomycin, 250 mg every six hours. Heparinization (5000 U. IV) was followed by insertion of a 6.8 mm or 7.5 mm OD LV cannula down the right common carotid artery. The assembled pump system was primed with saline, and all air bubbles were flushed out. This cannula was advanced into the left ventricle as monitored by a pressure strain gauge (Statham P37) connected to the pump which was attached to the cannula by a 36 inch length of $\frac{3}{4}$ " OD polyurethane tubing. Following satisfactory LV positioning of the inflow catheter tip, the pump outflow cannula (same OD as inflow cannula) was inserted into the left common carotid artery (Fig. 4). Pump flow at low rates (1 to 2 L/min) was started simultaneously with release of occluding clamps on the outflow tubing section. Once the preparation was hemodynamically stable at low flow rates, the animal, previously placed in a cargo net-sling, was lifted into the upright position, placed on a specially designed mobile stanchion equipped with a load cell for continuous weight measurements, and permitted to regain consciousness.

No additional heparin was administered. The animal was permitted to eat and drink at will. Diuretics were administered as necessary to maintain the animal's weight at a constant.

The pump was operated continuously at 6000 rpm, and pumped from 3 to 6 L/min. This was generally less than the calf's cardiac output, which super-imposed a normal arterial pressure contour on the pulseless pump output. At the conclusion of 24 hours of continuous perfusion, the calf was heavily sedated and the pump system removed, with ligation of the common carotid arteries bilaterally. At the conclusion of all experiments, whether completed at 24 hours or interrupted for any reason prior to that time, the pump system was immersed in 1% glutaraldehyde isotonic Ringer's fixative, buffered to pH 7.4, and kept in this solution for 24 hours. The pump was then disassembled and photographed. Any areas in which gross clotting was visible were examined by scanning electron microscopy (Cambridge Stereoscan, Model S-2). The arterial and venous monitoring catheters were also removed, and the animal returned to its pen. At one week after termination of the perfusions, the animals were sacrificed and complete autopsies performed, with particular emphasis on the status of the interior of the left ventricle, the cusps of the aortic valve, and evidence of peripheral arterial emboli. Specimens of all or obviously abnormal areas were obtained for fixation, staining and light microscopic study.

Blood samples were obtained prior to the onset of perfusion and at 4 hour intervals thereafter for the following analyses: hematocrit, white blood count, platelet count, prothrombin time, partial thromboplastin time,

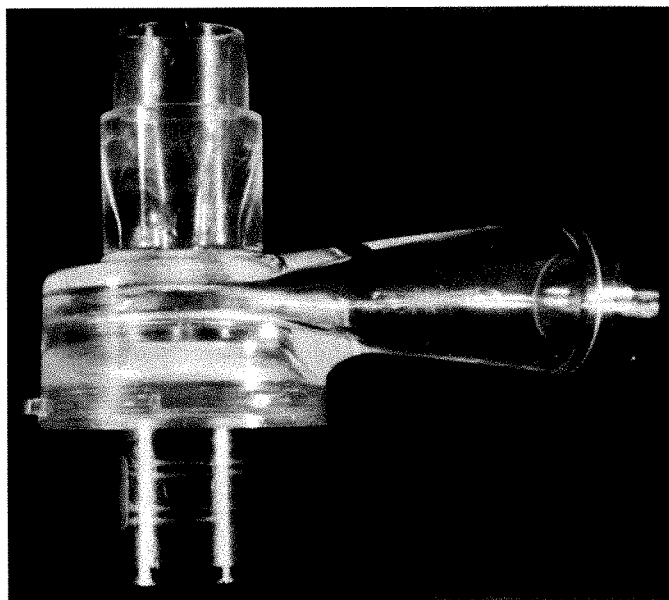


FIG. 2. The assembled pump measures $10 \times 9 \times 4$ cm and weighs 150 grams. It is driven by an external rotating magnetic field in the drive unit.

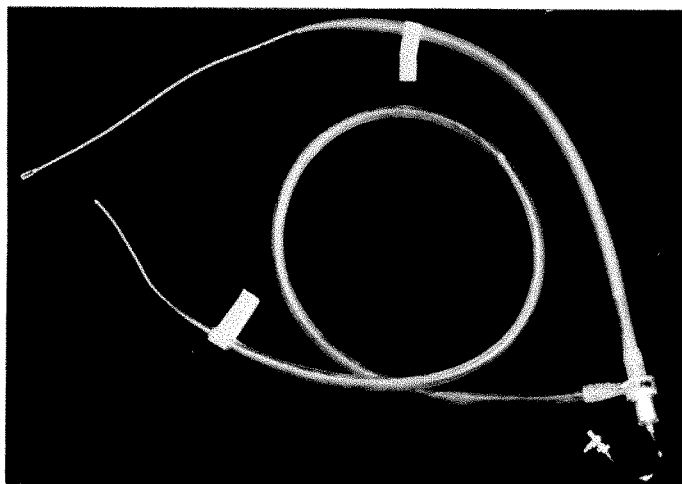


FIG. 3. The pump is shown together with the catheter system for left ventricular bypass. The upper catheter is the ultra-thin walled wire-wound and polyurethane-coated left ventricular cannula, which is inserted via the right common carotid artery in the calf, and is designed for insertion in the axillary artery in clinical applications. It is connected to a length of $\frac{3}{4}$ inch polyurethane tubing, the pump, another outflow length of tubing, and the arterial return catheter. All blood contact surfaces are of non-thrombogenic polyurethane polymers.

Lee-White clotting time, plasma hemoglobin concentration, plasma fibrinogen concentration, the presence of fibrin split products, and the position of the oxyhemoglobin dissociation curve.

B. Laboratory Methods

Hematocrit, white blood count and differential counts were performed by the method of Wintrobe.²² Platelets were counted in a Coulter Counter Model F as described by Harker and Finch,¹⁴ calibrated for calf platelets. The prothrombin time and partial thromboplastin times were

performed by the methods of Langdell,¹⁶ and the Lee-White clotting times were measured as described by Harper.¹⁵ The plasma hemoglobin concentration was measured in a Gilford Model 2400-S Spectrophotometer, by a modification of the method of Flink and Watson.¹² Plasma fibrinogen was measured by the technique of Biggs and Macfarlane,⁵ and the presence of fibrin split products was assayed by a modification of the tanned red cell agglutination technique of Merskey,¹⁷ using an antibody to calf red cells. The position of the oxyhemoglobin dissociation curve was ascertained with a Radiometer DCA-1 dissociation curve analyzer, according to the technique of Duvelleroy.¹¹

Results

Seven of the 55 calf implantation experiments were performed to obtain acute hemodynamic information, and were electively terminated in 8 hours or less without difficulty, and without obtaining hematologic data. Of the remaining 48 experiments, 28 were discontinued prior to 24 hours, as a result of mechanical construction faults (7), technical aspects of pump insertion or connection (7), separation or improper adhesion of the polyurethane pump lining elastomer (5), clot formation (5), and calf disease (4). However, these problems were generally limited to the early experiments. Successful 24 hour perfusions occurred only once in the first 10 experiments, but because increasingly more common as earlier problems were corrected and more experience in managing the calf preparation was obtained. Eleven of the last 14 experiments were carried out for the full 24 hours without mishap. In all, 20 perfusions were continued for 24 hours, with decannulation at that time and prolonged survival of 13 calves for one week following perfusion, with subsequent elective sacrifice.

Details of the hematologic data obtained from the 20 animals undergoing 24 hour perfusions are summarized in Table 1. They indicate a gradual decrease in hematocrit, from a mean of 37 to 31% in 24 hours, and a slight elevation in the WBC count from 8,800 to 10,800 during that time. The platelet count decreased in almost every animal, from an average control value of 594,000/mm³ to an average of 325,000/mm³ at 24 hours. Since heparin was administered only during the insertion of the pump system, the prothrombin time, partial thromboplastin time and Lee-White clotting time indicated disappearance of the heparin effect, which usually occurred within 4 hours of the start of perfusion. All 3 of these tests remained essentially constant and in the normal range throughout the remainder of the 24 hour perfusion period.

Hemolysis was well within tolerable limits in all but 2 of the experiments (numbers 2 and 7 in Table 1) in which 24 hour values over 300 mg% were correlated with the observation of clot formation on the rotor bearing and inadequate bearing perfusion with saline. In the 20 experiments lasting 24 hours, the final plasma hemoglobin av-

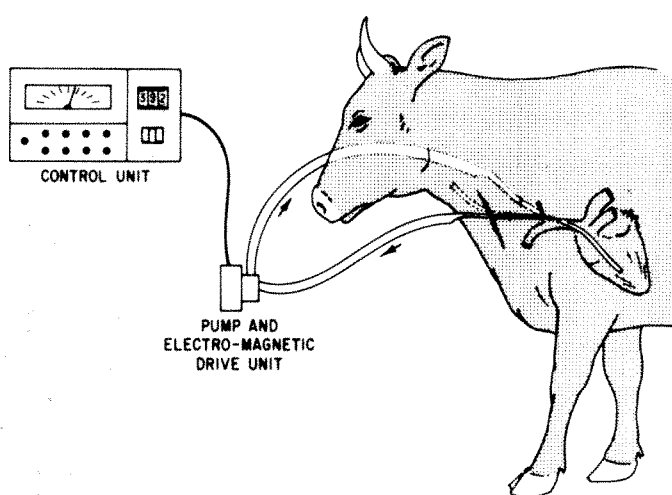


FIG. 4. Scheme of the calf perfusion preparation, in which the left ventricle is cannulated via the right common carotid artery, and arterial return is brought to the left common carotid artery. Despite distal ligation of both common carotid vessels, calves awoke from general anesthesia rapidly, and behaved normally during the perfusion and post-perfusion periods of observation.

TABLE 1. Hematologic Data from 24 Hour Calf Perfusion

Expt. No.	Hematocrit (%)		WBC ($\times 10^3/\text{mm}^3$)		Platelets ($\times 10^3/\text{mm}^3$)		Proth. Time (sec)		PTT (sec)		Plasma Hb (mg/dl)		Fibrinogen (mg/dl)		Lee White (min)		P ₅₀ (mm Hg)		Fibrin Split P. (Dilution)	
	C*	F**	C	F	C	F	C	F	C	F	C	F	C	F	C	F	C	F	C	F
1	-	52	7.6	16.7	855	478	14.2	32.5	55.8	>200	140	95								
2	48	44	14.2	9.3	236	450	14.0	14.4	36.8	42.9	44	464								
3	46	44	11.2	9.3	420	450	15.2	14.4	45.9	42.9	5	56								
4	43	40	14.2	14.5	478	308	14.9	13.4	31.6	58.1	2	22								
5	47	36	6.4	5.4	130	160	14.6	15.9	41.4	48.2	19	12								
6	38	37	5.2	1.5	537	270	19.5	22.1	41.3	43.4	17	19	465	415	8	11				
7	37	39	4.2	2.0	510	152	18.5	29.5	45.2	54.5	30	364	185	150	12	9	31.2	26.6		
8	32	37	8.0	3.2	595	125	21.0	29.0	32.0	42.0	0	0	370	260	8	8.0	29.1	28.6		
9	31	10	5.9	0.7	637	75	21	32	34.2	76	7	1	370	340	8	16.0	27.4	29.5		
10	34	15	4.4	3.5	615	85	17	52	41	300	0	50	420	400	6	11	28.0	25.4		
11	33	34	9.4	17.8	662	210	18.6	21.5	27.2	47.2	10	46	570	460	7	9	25.4	23.0		
12	39	37	11.5	37.4	951	619	14.9	13.5	67	69	19	18	-	-	6	7	-	-		
13	29	25	4.8	4.0	605	370	19.6	21.3	40.7	44.9	0	0	660	625	14	9	28.8	28.2	4.36	4.28
14	33	28	5.3	10.1	700	262	19	21.8	39.4	47.9	0	82	405	430	10	8	28.2	30.5	2.14	8.56
15	42	35	5.6	5.9	354	304	12	17.6	47	75.0	4	7	-	-	13	30	-	-	-	-
16	37	28	12.9	15.1	975	717	23.6	22.9	37	39.1	0	13	775	600	9	7	31.8	30.7	8.6	17.2
17	35	27	14.6	17.6	830	412	20.6	21.3	41.9	43.9	11	40	730	720	15	6	30.8	32.0	2.12	4.24
18	34	29	11.7	24.8	570	370	27.7	26.2	40.2	41.5	5	4	405	400	12	6	-	-	1.08	2.16
19	34	31	6.8	9.9	575	275	31.5	24.8	44.1	50.5	0	5	405	435	12	14	24.7	27.0	1.08	2.16
20	28	25	11.5	8.1	675	410	26.5	27.5	36.4	39.5	4	5	260	420	8	9	30.6	30.4	4.00	4.00

Mean 37 31 8.8 10.8 594 325 19.2 23.7 16 65 463 435 9.9 10.7 28.7 28.3 2.23 6.08

Data

Points 19 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20

*C = Control

**F = Final (24 hr)

eraged 65 mg%, and in the last 13 perfusions the final average plasma hemoglobin concentration was 21 mg%. Serum fibrinogen concentration was not altered significantly with a final mean of 435 mg% compared with the control mean of 463 mg%. No increase of fibrin split products to significant levels was demonstrated in any of the last 7 experiments, in which they were measured. Measurements of the oxyhemoglobin dissociation curve were performed in 11 perfusions and indicated no significant changes in this function.

Autopsies were performed on all animals either at the time of death or one week after pump removal. Cardiac arrest was initiated in the survivors by the injection of 50 cc pentobarbital and 5000 U heparin intravenously. The prominent gross autopsy findings were generally limited to the heart, great vessels, and kidneys.

In all calves examined immediately on discontinuation of perfusion, there was a thin, dark blue, cylindrical clot between the intima of the carotids and the outer wall of the wire catheter. This clot extended from the carotid arteriotomy centrally to the origin of the common carotid. This clot was uniformly present upon removal of the catheters, and at autopsy one week after perfusion had become an organized, well developed thrombus. In no instance did the thrombus extend proximal to the origin of the common carotid vessel. It should be noted that upon removal of the catheters, the carotid vessels were simply ligated proximal and distal to the arteriotomy. The aortic arch and distal aorta were uniformly free of damages and clots.

In the heart itself, vegetations were routinely seen on the surface of the tricuspid valve and presumably represented a septic process.

The right ventricle and pulmonary artery were normal. No clots were ever demonstrated in the left ventricle. In only one case did the endocardial surface of the left ventricle show areas of ecchymosis, attributed to trauma from the suction catheter.

The aortic valve cusps were remarkably free of evidence of trauma secondary to the suction catheter that transversed them. No vegetations were seen on the aortic cusps. In one instance the suction catheter slipped out of the left ventricle and lodged in the right sinus of Valsava, producing an instantaneous cardiac arrest.

The lungs were routinely normal, and no instances of pneumonia, atelectasis, or pulmonary embolism were observed.

Evidence of peripheral embolization was seen in 7 calves. Each of these was a small (1-15 mm) renal cortical infarct.

Finally, mild hepatomegaly and splenomegaly were observed in one animal and a moderate degree of each in one additional calf.

Discussion

Open thoracotomy was initially suggested as the means of initiating left heart bypass for support of the failing left

ventricle.⁶ The development by Dennis^{8,13} of a cannula which could be passed down the jugular vein and across the atrial septum into the left atrium made the procedure potentially available without a thoracotomy. Further experiments by Dennis and co-workers⁸ demonstrated a reduction of myocardial oxygen consumption when left ventricular bypass approached 100% of the cardiac output, but this was difficult to achieve using the left atrial cannulation technique.¹⁸ The further development by Zwart^{23,24} of a technique for the retrograde cannulation of the left ventricle by a catheter passed down the axillary or carotid artery and through the aortic valve led to the application of this approach to critically ill patients with left ventricular pump failure. Zwart demonstrated the ability of such a system to accept the entire cardiac output, and adequately decompress the left ventricle. In addition, the system was capable of maintaining adequate blood flow in sheep in spite of 12 hours of ventricular fibrillation, with easy eventual defibrillation and long-term animal survival.²⁴

Efforts at the development of prolonged LV bypass systems, both external and implanted, have recently been pursued by Bernhard² and Pierce¹⁹ and their groups, with comparable demonstrations of performance in substantially longer perfusions. However, the concept of a simple centrifugal, magnetically-driven pump with inherent autoregulatory features, high capacity, a single moving part, and all rigid construction with a complete non-thrombogenic blood surface lining, suggests that this pump system may prove simpler and more effective than the more complex devices previously described.

While the non-thrombogenic lining materials employed permitted experimental bypass for one day in the absence of continuing heparinization with subsequent prolonged survival, the demonstration of occasional thromboembolic events suggests the need for further efforts at identifying the source of such emboli, particularly in sites of defects in the lining material, or at areas of material junction. If we are unable to completely identify and eliminate all embolic generation areas, then eventual clinical trials of this system will require some degree of anticoagulant protection.

The important advantages of the system tested in the current experiment include the new thin-walled flexible non-kinking left ventricular cannula, which permitted easy access to the left ventricle without fluoroscopy, the non-thrombogenic lining of the entire system, which permitted prolonged pumping without anticoagulation, and the simplicity of the system with no reservoirs, low prime, and simplified controls. This compact, nonhemolytic system should permit long term extracorporeal left ventricular bypass without thoracotomy or continuous anticoagulation in the treatment of reversible left ventricular pump failure, with a simplified and effective cardiac support system.

Recent interest in decreasing the extent of myocardial

injury following coronary artery occlusion with various circulatory assist modalities has provided an additional stimulus for the development of simple and effective cardiac assistance systems, which can be inserted and removed with minimal surgical manipulation. DeLaria has confirmed the ability of the present system effectively to decrease the extent of myocardial ischemia following acute coronary artery occlusion in the dog.⁷ Thus, the demonstration of system safety and ease of insertion assumes even greater importance, since patients at lesser risks than those in acute cardiogenic shock may be considered appropriate candidates for perfusion in efforts to conserve marginally perfused myocardium.

One of the unresolved problems posed by the LV bypass system tested in these experiments is the question of tolerance to pulseless flow for prolonged periods of support. In the present experiments, pump flow rates averaged 4-5 L/min, and were always less than the total cardiac output of the calf (usually 6-7 L/min). Under these circumstances, the left ventricle continues to eject blood into the aorta with each contraction, and superimposes a pulse on the steady pump flow. Additional experiments to test the concept of total LV bypass and prolonged pulseless arterial perfusion are currently under way in our laboratory.

Conclusions

A left ventricular bypass system for temporary extracorporeal use has been developed and tested in 55 calf experiments. Advantages of this system include an ultrathin-walled catheter for transarterial cannulation of the left ventricle and a compact, centrifugal blood pump, with non-thrombogenic blood surfaces of pyrolytic carbon and a polyurethane elastomer. Twenty perfusions of 24 hours duration were completed with no heparin after the initial implantation dose. Gross thrombi or emboli were rarely found in the pump or autopsied calves, and hematological studies indicate mild and tolerable degrees of blood damage.

Acknowledgments

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Barium Granuloma of the Rectum:

An Uncommon Complication of Barium Enema

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Barium sulfate granuloma of the rectum may develop when this contrast material is forced through a discontinuity in the rectal mucosa. The ensuing mass may be confused with carcinoma. Preoperative biopsy and attention to plain films will prevent unnecessary inappropriate surgery.

INTUITIVELY, one would suspect that instillation of a foreign material, often under increased pressure, into a long feces lined tube, at times weakened by disease processes, would lead to frequent complications; the barium enema, in practice, however, remains a relatively safe "invasive" procedure. The most notable hazard encountered with this examination is colonic perforation with extravasation of barium sulfate or other contrast material into the peritoneal cavity or retroperitoneal space. In various reports this was seen in 2-4 cases per 10,000 examinations with an attendant mortality of approximately 50%.^{14,20} The degree of resultant damage appears to be proportional to the amount of associated fecal contamination.⁷ Other less frequent complications are inspissation of barium sulfate with resultant mechanical obstruction of the colon²⁶ sometimes resulting in barium appendicitis,⁸ venous embolization of barium,^{23,24} cardiac arrhythmias from colonic manipulation and barium granuloma of the rectum (see Table 1). This last complication is quite uncommon and less than 35 cases have been reported in the readily available literature. Four additional cases from the French and Belgian literature were mentioned in a reference article but were not reviewed for the current paper.²⁵ A further report of this complication is described below.

Case Report

A 46-year-old Negro man was well until 5 years prior to admission

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when peptic ulcer disease was diagnosed. Treatment with a bland diet and antispasmodics completely relieved his symptomatology. In February, 1970, he presented to the West Haven V.A. Hospital with a recent history of anorexia, early satiety and a 40 pound weight loss. He drank "several highballs" daily and one pint of whiskey on weekends. Pertinent physical findings on admission included hepatomegaly without other abdominal masses and a normal rectal examination. Five different stool specimens tested for occult blood were negative. An extensive x-ray work-up of the gastrointestinal tract revealed no evidence of neoplastic disease; an oral cholecystogram demonstrated cholelithiasis and a percutaneous liver biopsy was compatible with pericholangitis and cholestasis. The barium enema performed on 3/2/70 was reported as uneventful and the patient experienced no discomfort or bleeding during the procedure. A balloon catheter was used but an air contrast study was not performed. The patient was discharged on a high calorie diet with an admonition to omit alcohol.

He failed to keep follow-up appointments and again presented to this institution on 9/19/72 with the complaints of anorexia, weight loss, and hematochezia for 3 months. During this period he had up to 4 loose bowel movements per day, each interspersed with bright red blood. He denied abdominal pain, sense of incomplete evacuation, nausea, vomiting, melanotic stools, mucus, tenesmus, or bleeding between bowel movements. Pertinent physical findings included a 14 cm liver span by percussion, no abdominal masses, tenderness or other organomegaly and a firm 3-4 cm in diameter stony-hard mass with a slightly raised center on the right rectal wall at 6 cm from the anal verge. (Fig. 1) Mucus taken from this area was strongly positive for occult blood. Proctosigmoidoscopic examination revealed a 1 cm in diameter ulcerated lesion in the above location with slightly rolled up mucosa edges around its periphery. Suspecting carcinoma of the rectum, a barium enema was performed to rule out further lesions. Scout films without contrast revealed an irregular opaque density in the lower rectal wall (Fig. 2) Multiple biopsies of the lesion later revealed a granulomatous reaction around doubly refractile crystalloid material in the submucous and muscular layers of the rectal wall (Fig. 3) A cholecystectomy for his cholelithiasis was performed during this admission. Follow-up stools for occult blood have been negative and the patient denies further rectal bleeding.

TABLE 1. Complete Collection of the Cases of Barium Granuloma of the Rectum in the Literature

Author	Age, Sex	Balloon Used	Air Contrast	Pain	Blood	Rectal Pathology	Findings of BE	Interval	Location Description	Ulcer	Treatment
Beddoe ²	53M	NS	yes	no	NS	hemorrhoids	normal	3 wks	1 cm tumor posterior at 6 cm.	no	excision
Swartz ²⁹	56M	NS	NS	yes	NS	NS	NS	immediate	posterior anal mass with sinus tract	yes	excision
Gordon ¹⁸	25M	NS	NS	NS	NS	NS	normal	2 dys	0.5 cm tumor anterior at 5 cm.	no	biopsy
	62M	yes	yes on 1st NS on 2nd	NS	NS	hemorrhoids	normal	8 dys	0.5 cm tumor left lateral wall at 5 cm.	no	biopsy
	52M	yes	NS	NS	NS	NS	cecal diverticulum	5 dys	nodule 3 mm diameter, location NS	yes	biopsy
Levine ¹⁹	78F	NS	NS	NS	NS	"tender masses"	ulcer of rectal mucosa	unknown	large rectal plaque	no	abdomino-perineal resection
	63F	no	yes	yes	NS	NS	diverticula mid-sigmoid	4 dys	anterior ulcer at 7.5 cm	yes	biopsy
McCurdy ²²	63F	NS	NS	NS	NS	none	normal	1 wk	anterior ulcer at 6 cm	yes	drainage
Burnikel ¹⁴	43M	NS	NS	yes	NS	NS	NS	immediate	left lateral wall perianal induration	no	excision
	47M	NS	NS	yes	NS	NS	NS	4 dys	perianal abscess	no	I & D
Carter ⁶	69F	yes	NS	no	NS	NS	diverticulosis	1 wk	anterior, (R) lateral & posterior-lateral	yes	biopsy
Dubarry ¹⁰	41M	no	NS	no	NS	none (past history amyotrophic lateral sclerosis)	notched appearance of sigmoid	immediate	proctitis with scattered barium flecks	no	biopsy
Rand ²⁷	69M	yes	NS	NS	NS	none	NS	19 dys	posterior right 2.5 x 8.0 cm ulcer at 8 cm	yes	biopsy
	76M	yes	NS	NS	NS	none	carcinoma of sigmoid	1 mon	anterior 1 x 2 cm ulcer at 7 cm	yes	biopsy
	72F	yes	NS	NS	yes	none	NS	1 mon	rectovaginal fistula at 7.5 cm	—	debridement

TABLE 1 (continued)

Author	Age, Sex	Balloon Used	Air Contrast	Pain	Blood	Rectal Pathology	Findings of BE	Interval	Location Description	Ulcer	Treatment
Bernier ³	73F	NS	NS	NS	NS	NS	NS	1 wk	2 × 4 cm necrotic sac-like lesion at 4 cm	yes	autopsy
Poinot ²⁵	80F	yes	NS	yes	NS	NS	NS	immediate	anterior linear tear rectal pouch	yes	biopsy
Gaston ¹⁵	60M	no	no	no	no	NS	normal	14 mon	2 cm diameter tumor (sessile)	no	biopsy
	10M	no	no	yes	no	recent rectal biopsy (history ulcerative colitis)	normal	immediate	anal verge rectorectal abscess	no	I & D
Lull ²¹	78M	NS	NS	NS	NS	NS	NS	45 dys	anterior 2 × 3 cm lesion at 4 cm	yes	biopsy
Faivre ¹³	77F	yes	NS	NS	NS	NS	normal	4 mon	left lateral ulcer upper rectum	yes	biopsy
	80F	yes	NS	yes	NS	NS	NS	immediate	left lateral 4 × 6 cm ulcer rectum	yes	biopsy
	60F	yes	NS	yes	yes	NS	NS	immediate	ulcer above anal sphincter	yes	biopsy
Diakonov ⁹	49F	NS	NS	yes	NS	periprocitis	NS	several days	posterior perirectal abscess at 5 cm with sinus tract	NS	I & D excision tract
Altobelli ¹	73F	yes	no	yes	NS	mucosal ulcers	diverticulosis	immediate	7-10 cm "polypoid" area recto-sigmoid and rectovaginal fistula	no	transverse colostomy
Weitzner ²¹	39M	NS	NS	NS	NS	rectal mass	normal	7 dys	4 mm diameter lesion above anal verge	NS	biopsy
	75M	NS	NS	NS	NS	cancer of rectum	normal	7 dys	4 mm diameter polypoid lesion at 15 cm	NS	biopsy

TABLE 1 (continued)

Author	Age, Sex	Balloon Used	Air Contrast	Pain	Blood	Rectal Pathology	Findings of BE	Interval	Location Description	Ulcer	Treatment
	71M	yes	NS	NS	NS	NS	normal	18 dys	anterior 3 × 12 mm lesion at 8 cm	NS	biopsy
Carney ³	38F	NS	NS	NS	NS	old recto-vaginal fistula	ulcerative colitis	7 dys	opaque white substance in submucosa of rectum & (L) colon	NS	procto-colectomy
Lewis, <i>et al.</i>	46M	yes	no	no	no	none	normal	2.5 yrs	(R) 4 cm in diameter mass at 6 cm	yes	biopsy

Note: NS = not stated. Balloon used, air contrast, pain, blood and findings refer to techniques and/or findings during the barium enema which caused the granuloma. Rectal pathology, when stated, refers to associated rectal findings at that time. Interval—time between barium enema and granuloma symptoms; Location/Description—author's description of the granuloma; Ulcer—whether an ulcer was present on rectal wall; Treatment—treatment to the granuloma.

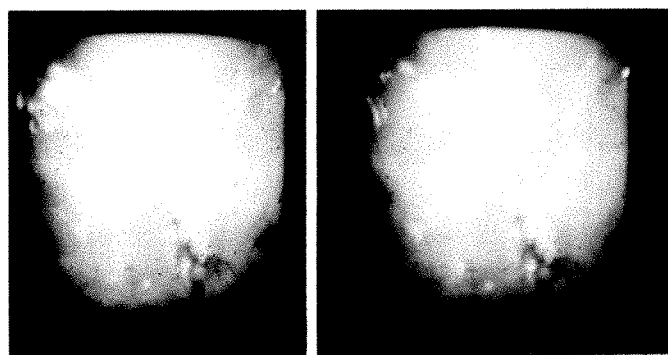


FIG. 1. Endoscopic view of barium granuloma of the rectum.

Discussion

Barium sulfate granulomata of the rectum develop when this contrast material is forced through a discontinuity in the rectal mucosa into the subjacent layers. This break in continuity may result from intrinsic disease such as amebiasis or ulcerative colitis or more commonly by injury from insertion of the enema tip, overinflation of the enema balloon, proctosigmoidoscopy, or rectal biopsy.^{18,30} Injury may not be apparent at the time of examination since only 10 of the cases reviewed in Table 1 experienced undue discomfort. In fact, one patient inserted the enema catheter himself without difficulty.¹⁰ The majority of granulomata developed between 4-8 cm from the anal verge on either the anterior or posterior wall, thus giving evidence to the assumption of enema catheter injury in its pathogenesis. The extravasated barium may remain confined to a limited portion of the submucous space without symptoms or dissect through the venous layers of the rectal wall causing necrotizing proctitis, perirectal abscesses, or draining sinus tracts. Regardless of location, the free barium incites a variable inflammatory reaction resulting in the initial outpouring of polymorphonuclear leukocytes. By the end of a week, if no complications have developed, elements of a chronic inflammatory reaction appear marked by fibroblastic proliferation resulting in various degrees of fibrosis, macrophages and multinucleated foreign body giant cells with intracytoplasmic barium sulfate crystals.¹⁷ As time passes this process can evolve into a typical granulomatous process microscopically.

The individual lesions in the reported series varied considerably, ranging in size from 2-3 mm polypoid masses to extensive necrotic ulcers up to 10 cm in diameter. In most cases no pre-existing rectal pathology was demonstrated or mentioned. Although most granulomata appeared between 4-8 cm from the anal verge, 7 were located in the perianal region and one was found at 15 cm.

Barium granuloma gains significance since it can mimic carcinoma of the rectum. Occult blood can be shed in the stool if the lesion has ulcerated and digital examination

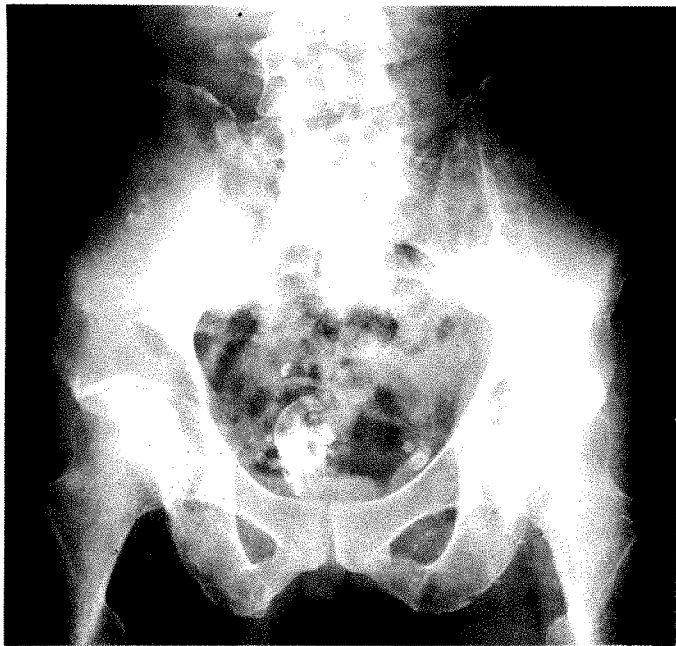


FIG. 2. Radiographic view of barium granuloma of the rectum.

may reveal a shaggy, firm intrinsic mass. Biopsy and the finding of contrast material in the tissues on plain roentgenography of the suspicious area will reveal the true nature of the lesion although two patients in the series underwent major surgical procedures because of the continued suspicion of carcinoma (a sigmoid colostomy and abdominoperineal resection respectively).

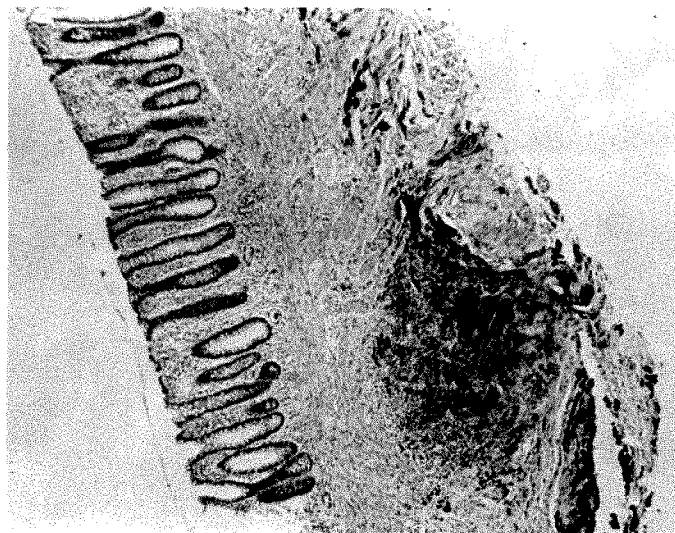


FIG. 3a. A microscopic view of barium granuloma of the rectum: low power ($\times 62$).

Treatment in the majority of cases involved excisional biopsy through the proctosigmoidoscope or establishment of drainage if suppuration were present. Experimentally, excision of overhanging mucosal edges around the barium granuloma resulted in delayed healing.²⁷ Enlargement of the site of perforation with excision of only necrotic debris resulted in the most expeditious healing. It was also demonstrated that re-epithelialization would occur despite the continued presence of barium crystals in the underlying tissue. To date there has been no

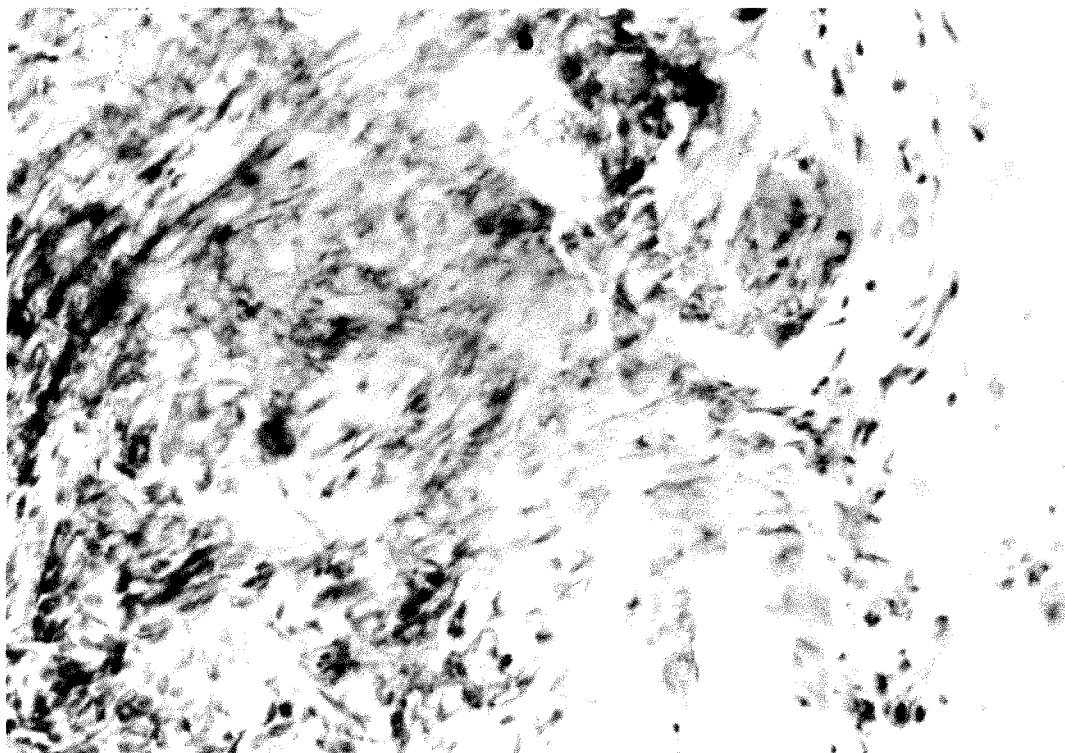


FIG. 3b. Microscopic view of barium granuloma of the rectum: high power ($\times 340$).

documentation of carcinoma arising from an old barium granuloma.

The major complications of barium extravasation seemed to occur when large volumes of contrast material were extruded into the rectal wall or adjacent tissues. A barium enema performed in a 69-year-old woman for the evaluation of a rectal polyp resulted in perforation of the rectum with extravasation of contrast material into the retroperitoneal space.³⁰ A sigmoid colostomy with drainage of the perirectal space provided interim control but 6 weeks later urinary retention progressing to anuria developed. Re-exploration revealed a dense perivesical fibrosis due to a barium granuloma and indwelling ureteral catheters were required to maintain urinary flow. From the French literature, a barium enema performed for the evaluation of diarrhea in an elderly man resulted in rectal perforation with dissection of contrast material upward into the free peritoneal space resulting in peritonitis and death.³ An unusual case of extrarectal escape of barium complicating barium enema was recently described where no perforation site was demonstrated either clinically or at autopsy.²⁸ It was postulated that although an initial submucosal injection of contrast might have occurred, dissemination was along the lymphatic system with subsequent infection of the retroperitoneal space.

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Axillary-Femoral Bypass Graft Patency Without Aorto-femoral Pressure Differential:

Disuse Atrophy of Ipsilateral Ileo-femoral Segment

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Differential aorto-femoral pressure gradient is not required to assure axillary-femoral bypass graft patency for a brief period of time. One-hundred twenty-three days elapsed from axillary-femoral graft construction to elective removal of the functioning conduit in an individual without aorto-femoral pressure differential. During this time, reversible "disuse atrophy" of the ipsilateral ileo-femoral arterial system occurred. It is suggested that *phasic* differences in pulse wave propagation between the aorto-iliac-femoral and axillary-femoral circuits maintained graft patency and accompanying decreased flow volume in the ileo-femoral arterial circuit resulted in "disuse atrophy."

Axillary-femoral grafting as a means of extra-anatomic bypass has gained popularity since first introduced in the United States by Blaisdell and Hall in 1963.² It has proven useful in restoring lower extremity circulation after removal of infected aortic prostheses and in selected poor risk patients with rest pain or gangrene.⁷ Efficacy of this procedure, long-term patency results, and indications for its use have been documented by several reports. Information is non-existent, however, concerning the interval of time axillary-femoral grafts remain patent in the absence of aorto-femoral pressure gradients. Two recent reports indicate doubt that axillary-femoral grafts remain patent for even a period of hours without a differential pressure gradient.^{4,5}

The purpose of this report is to document axillary-femoral graft patency without aorto-femoral differential pressure gradients. Prosthetic function continued for 123 days before elective removal. In addition, serial arteriograms over this interval documented ipsilateral ileo-femoral arterial "atrophy." This phenomenon reversed following elective removal of the axillary-femoral graft.

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Case Report

A 25-year-old man developed a supraceliac pseudoaneurysm of the abdominal aorta four months after a gunshot wound to the abdomen. He had lost 45 pounds from the time of injury to admission to the University of Kentucky Medical Center. He appeared chronically ill and was septic, with spiking daily temperatures to 38.8 C. Doppler measurements of brachial and posterior tibial artery pressures were essentially equal (Table 1). Chest x-rays documented left pleural fluid. Supraceliac pseudoaneurysm of the abdominal aorta was documented by aortography. Common iliac arterial diameters, one centimeter distal to the aortic bifurcation, each measured 11 mm (Fig. 1A). Diagnosis of an infected post-traumatic supraceliac pseudoaneurysm was made.

On September 28, 1973, a right axillary-femoral bypass graft was constructed using a one cm diameter knitted Dacron prosthesis (Fig. 2). Postoperative measurements of brachial and posterior tibial artery pressures remained equal (Table 1).

Three days following construction of the axillary-femoral bypass, definitive repair of the supraceliac pseudoaneurysm was accomplished by partial excision of the aneurysm and tangential aortorrhaphy. The axillary-femoral graft was not removed. It continued to function.

Percutaneous left axillary aortography, performed 9 days after operation documented satisfactory repair of the aorta. Decrease in diameter of the right common iliac artery from 11 mm to 9.5 mm was noted (Fig. 1B) (Table 2). The left common iliac artery measured 11 mm. Doppler measurements of brachial and posterior tibial arterial pressures remained essentially equal with the axillary-femoral graft both patent and digitally occluded (Table 1). The patient was released from the hospital on the eleventh postoperative day.

Three months later, he was readmitted to the University of Kentucky Medical Center for elective removal of the axillary-femoral graft.

The patient appeared well and had no complaints. He had gained 26 pounds. The axillary-femoral graft continued to pulsate. Doppler measurements of brachial and posterior tibial arterial pressures remained comparable (Table 1).

Percutaneous left femoral retrograde aortography was performed with injection of contrast material into the aortic arch. Satisfactory appearance of the abdominal aorta was documented (Fig. 3). Direction of axillary-femoral graft flow was determined by evaluating sequential

TABLE 1. Doppler Arm and Ankle Arterial Pressure Measurements (mm Hg)

	Brachial		Posterior Tibial	
	Right	Left	Right	Left
Pre Ax-Fem	124	124	120	120
Post Ax-Fem 10/1/73	112	112	112	112
Post Ax-Fem; Post Aortorrhaphy				
Ax-Fem Open 10/5/73	120	120	118	118
Ax-Fem Occluded	120	120	114	114
Ax-Fem Open 1/18/74	112	112	112	112
Ax-Fem Occluded	112	112	108	108
Post Removal Ax-Fem	118	118	116	116

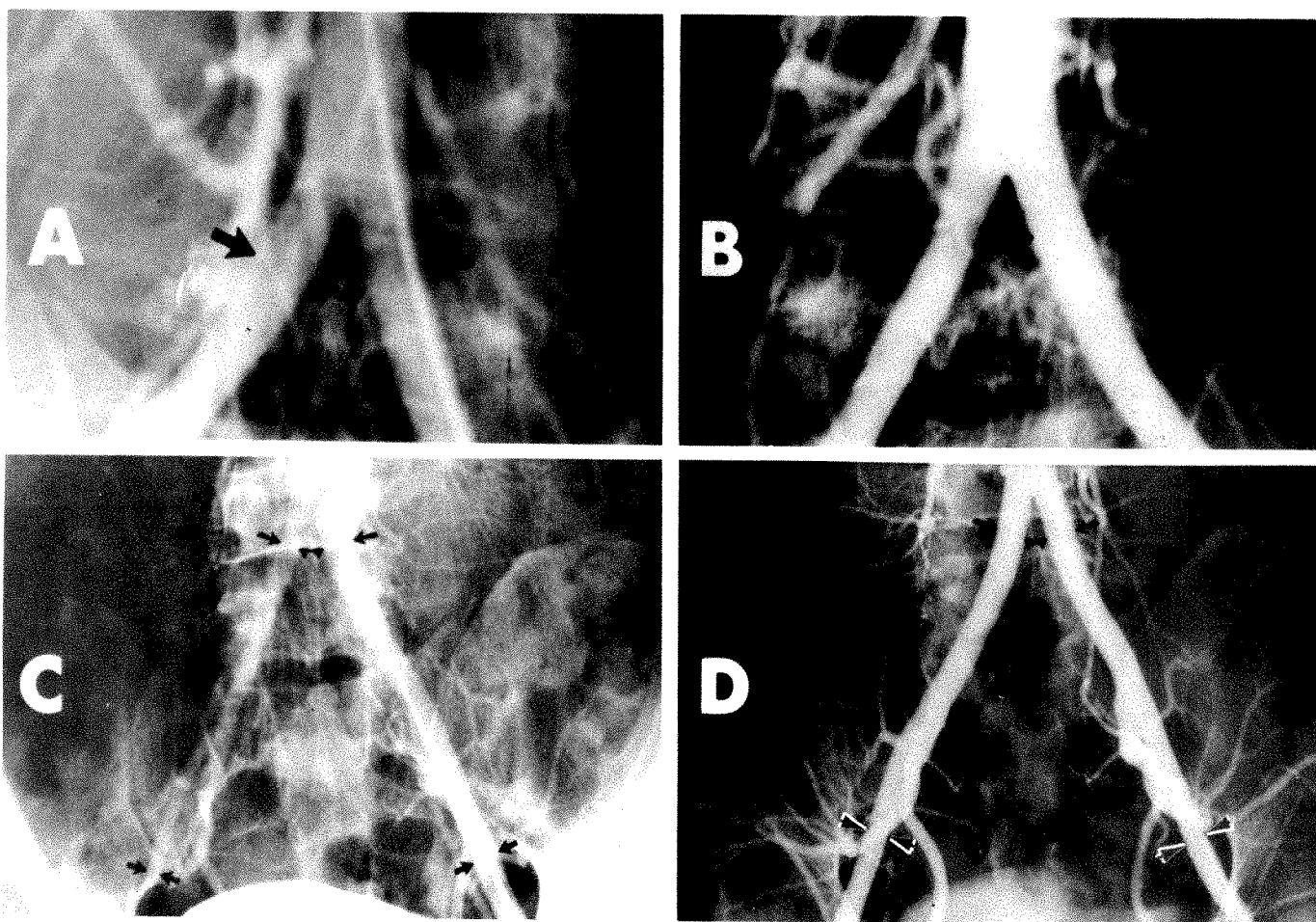
Direct Aortic Pressure Measurements (mm Hg)

	Pulsatile Pressure	Mean Pressure
T12—above Aortorrhaphy	104/50	68
L3—below Aortorrhaphy	100/52	68

TABLE 2. Iliac and Femoral Arterial Diameters (Millimeters)

	Common Iliac		External Iliac-Femoral	
	Right	Left	Right	Left
Preoperative 9/25/73	11	11	—	—
Post Ax Fem 10/10/73	9.5	11	—	—
Post Ax Fem 1/26/74	8.5	11	6	10
Post Removal Ax Fem 6/28/74	11	11	10	10

films following contrast injection. Flow was toward the lower extremities in the axillary-femoral graft. Posterior indentation of the aorta opposite the bullet at the celiac axis level was seen on lateral views (Fig. 3). Direct measurements of mean aortic pressures at vertebral bodies T12 and L3, proximal and distal to this defect, were each recorded at 68



FIGS. 1A to D. (A) Preoperative aortogram showing right and left common iliac arterial diameters. Arrowheads denote equal diameters. (B) Aortogram nine days after repair of supraceliac aorta. Right common iliac artery has decreased in diameter. Left common iliac artery has not changed. (C) Aortogram, including ileo-femoral arterial segments, prior to axillary-femoral graft removal. Arrowheads denote further decrease in diameter of right ileo-femoral system. Left ileo-femoral system remains unchanged. (D) Aortogram six months following axillary-femoral graft removal. Right and left ileo-femoral systems are identical and equal to preoperative dimensions.

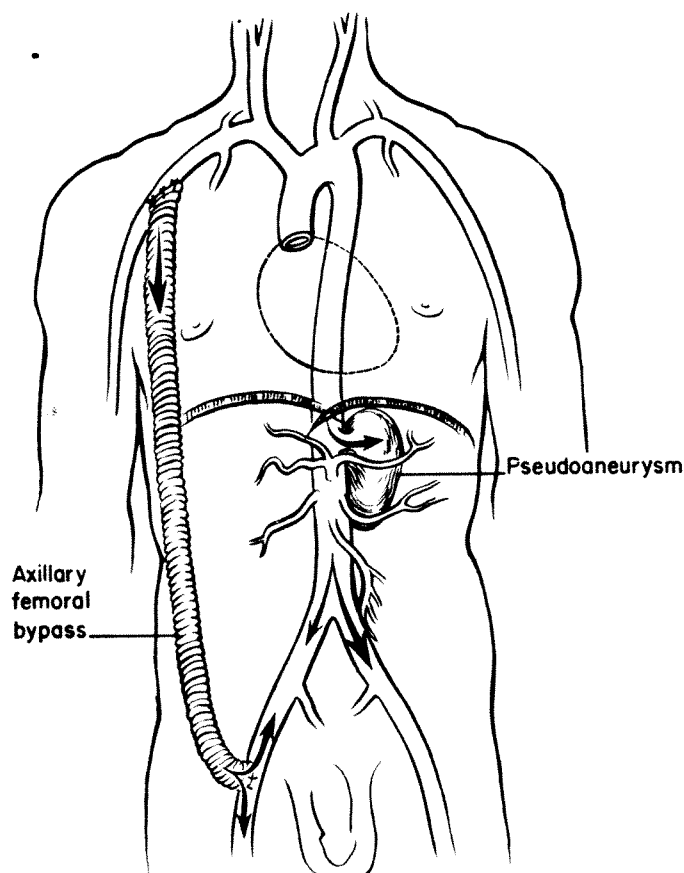


FIG. 2. Supraceliac pseudoaneurysm and preliminary axillary-femoral bypass. Vector arrows indicate directions of blood flow.

mmHg (Table 1). Wave forms of each pressure recording were similar. Right common iliac arterial diameter measured 8.5 mm, one centimeter distal to the aortic bifurcation. Left common iliac arterial diameter measured 11 mm at a similar level. Right and left external iliac arterial diameters measured 6 mm and 10 mm respectively (Fig. 1C) (Table 2).

On January 28, 1974, 123 days following construction of the right axillary-femoral bypass, it was removed. At operation it was patent and functioning. The patient made an uneventful recovery and was released on the third post-operative day.

Upon his third admission to the University of Kentucky Medical Center in June, 1974, he was well, and had returned to full employment. Percutaneous left femoral retrograde aortography was performed. Common iliac arterial diameters one centimeter from the aortic bifurcation each measured 11 mm (Fig. 1D). Similarly, external iliac arterial diameters were identical, each measuring 10 mm (Table 2).

Discussion

Blaisdell and his colleagues in a 1965 report documented patency of a right axillary-femoral graft for 28 days during staged treatment of an abdominal aortic aneurysm.³ They did not measure for aorto-femoral pressure differential. Concomitant femoral-femoral bypass grafting with ligation of the left femoral artery proximal to the anastomosis was also performed in their patient. This prevented premature clotting of the femoral-femoral prosthesis. The right femoral artery was not ligated in the hope that spontaneous thrombosis of the right common iliac artery might occur. The potential gradient from such manipulations probably maintained axillary-femoral graft patency. Finseth and Abbott temporarily occluded external iliac arteries bilaterally proximal to the distal anastomoses of a composite descending aortic left and right iliac artery bypass to ensure continued flow through the grafts during repair of a mycotic abdominal aortic

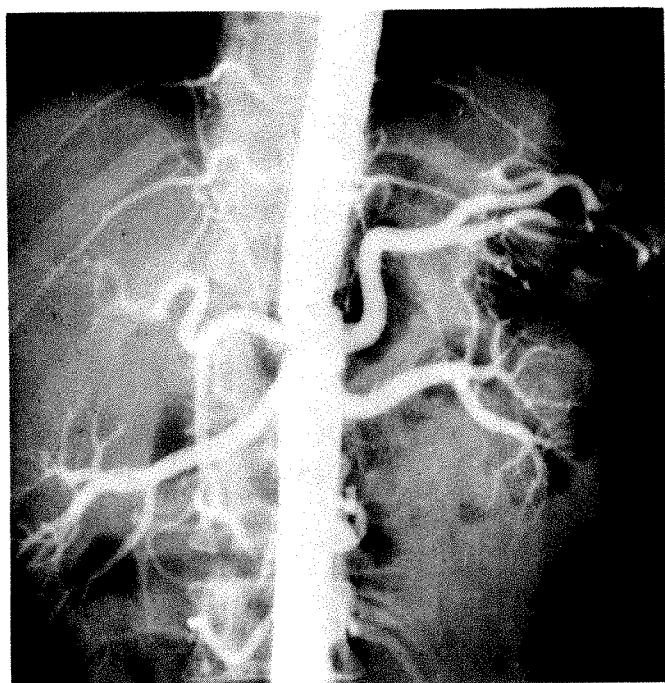


FIG. 3. Postoperative appearance of repaired supraceliac aorta. (left) AP projection documents satisfactory appearance with all visceral branches patent. (right) Lateral view showing posterior aortic indentation opposite bullet.

aneurysm.⁵ Similarly, Cooke and Ehrenfeld left an arterial clamp *insitu* on the right common femoral artery proximal to the femoral anastomosis of an axillary-femoral bypass graft to avoid aorto-iliac competitive flow and possible graft occlusion during repair of a mycotic abdominal aortic aneurysm.⁴ In addition, Barker commented that a true differential pressure is needed to maintain flow through an axillary-femoral prosthesis but did not indicate the time interval the graft might remain patent without significant gradient.¹

One-hundred twenty-three days elapsed from insertion to removal of the right axillary-femoral graft in the patient reported herein. At the time of elective removal, it was still widely patent and functioning. That no significant gradient across the aortic repair existed is evident by examining pressure data obtained during followup aortography and comparative brachial-posterior tibial artery pressure data obtained by Doppler measurements (Table 1). Clearly, axillary-femoral bypass grafts may remain patent for at least 4 months without pressure gradients across the aorto-femoral system in young individuals. Maneuvers to prevent competitive parallel flow do not appear necessary for continued axillary-femoral graft function for this brief time period.

Prior to removal of the axillary-femoral graft, retrograde aortography confirmed satisfactory appearance of the paraceliac aorta (Fig. 3). At that time, the diameter of the right common iliac arterial segment measured 8.5 mm, whereas prior to construction of the axillary-femoral graft, it measured 11 mm. This represents a 2.5 mm decrease in diameter. The left common iliac artery measured 11 mm on all studies (Table 2). The reason for this diminution in size of the right common iliac arterial segment is unclear, but "disuse atrophy" phenomenon is a distinct possibility.

Even though "atrophy" of the right ileo-femoral system occurred, it was not hemodynamically significant since Doppler ankle pressure measurements did not differ significantly from brachial pressure measurements with the axillary-femoral graft patent and digitally occluded (Table 1). Examination of serial films following contrast injection into the aortic arch clearly showed that flow down the axillary-femoral graft "led" flow in the ileo-femoral systems. Contrast material appeared in the distal axillary-femoral system before it appeared in the left ileo-femoral system. Contrast in the right iliac system was not seen at this time but did become evident in later films. Resulting opposing streams from the aorta and right axillary-femoral graft caused to-and-fro surging of blood in the right iliac system (Fig. 2). An explanation for this phenomenon may be the phasic differences in pres-

sure waves in the aorto-ileo-femoral system and axillary-femoral graft. The more distensible the conduit wall, the slower the propagation of the pulse wave.⁶ Since the axillary-femoral Dacron conduit was less distensible than the elastic host arteries, the pulse wave in the axillary-femoral graft was *physically* ahead of the pulse wave in the aorta. Resulting differences in pulse wave propagation caused axillary-femoral flow to precede aorto-iliac flow. Not only did this maintain axillary-femoral graft patency for 123 days, but reciprocating right iliac flow may have induced arterial "atrophy."

Evidence is abundant that net increased volume flow causes proximal arterial dilatation in an arterial-venous fistula circuit. Surging flow of opposing streams of the right ileo-femoral and axillary-femoral systems prevented thrombosis of the ileo-femoral system but decreased net volume flow in either retrograde or antegrade directions. Under such conditions the converse of the consequences of increased net volume flow pertain and "atrophy" of the affected conduit occurred.

Arteries of young people are apparently responsive and resilient enough to accommodate varying flow volumes. "Atrophy" of the ileo-femoral system of the patient reported herein was a reversible phenomenon. Six months following removal of the axillary-femoral prosthesis the diameter of the right ileo-femoral system was identical to the left and the same as preoperative (Table 2). Just as proximal arterial expansion following repair of an arteriovenous fistula in young people is reversible, so is arterial "atrophy" reversible as illustrated by the patient reported herein. Whether the right ileo-femoral system would have progressed to occlusion is unknown, but by examining serial arteriograms it appears that ultimate occlusion might have occurred.

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Diagnosis of an Enteric Duplication with Pertechnetate ^{99m}Tc Scanning

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A case of enteric duplication is reported in which preoperative pertechnetate ^{99m}Tc scanning demonstrated localized uptake in the region of the anatomic abnormality. This test is recommended for use in the evaluation of lower gastrointestinal bleeding in infants and children.

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ABDOMINAL SCINTISCANNING following administration of the radiopharmaceutical pertechnetate ^{99m}Tc has recently been shown to facilitate the preoperative diagnosis of bleeding Meckel's diverticulum.³ Since ^{99m}Tc is metabolized much like the chloride ion, it is actively concentrated and secreted in gastric mucosa, presumably by parietal cells. In those patients having ectopic gastric tissue within a Meckel's diverticulum, abdominal scanning may demonstrate localized uptake of the radionuclide over the anatomic anomaly. Increased local uptake of ^{99m}Tc has also been described in other conditions characterized by the presence of ectopic gastric mucosa, such as Barrett's esophagus¹ and intrathoracic gastrogenic cysts.⁴ We have recently employed scanning with pertechnetate ^{99m}Tc in the preoperative evaluation of a child with rectal bleeding, and certain unique features of this case have prompted the following report.

Case Report

An 11-month-old Caucasian boy was seen at an outside hospital after passing a large amount of bright red blood and clots per rectum. His admission hematocrit was 19%, but following whole blood transfusion, his clinical course stabilized and no further bleeding occurred. He was transferred to the North Carolina Memorial Hospital where physical examination disclosed no abnormality. There was no abdominal tenderness or palpable mass.

The patient had been born after an uncomplicated full-term pregnancy, and on the first day of life a small right-sided abdominal mass was palpated. Evaluation at that time including barium enema examination, upper gastrointestinal series, and abdominal arteriography demonstrated no abnormality, and the mass was no longer palpable when

the child was discharged at five days of age. His parents were informed that the patient might have an "extra growth of the intestine," but on routine follow-up visits, the mass was not palpable and the child had remained well.

Following admission to our hospital, barium enema examination revealed extrinsic pressure on the medial aspect of the cecum (Fig. 1). Barium examination of the upper gastrointestinal tract and small intestine showed no abnormality, but a flat film of the abdomen 24 hours later disclosed an accumulation of barium in a mucosa-lined cavity in the right lower quadrant (Fig. 2). Subsequent ^{99m}Tc scan demonstrated an area of increased activity in this region which was felt to represent a large Meckel's diverticulum or an intestinal duplication (Fig. 3).

Exploratory celiotomy disclosed a 4×5 cm saccular enteric duplication along the mesenteric border of the ileum approximately 15 centimeters from the ileocecal valve (Fig. 4). The duplication and attached ileum were resected, and an end-to-end ileoileostomy was performed. The postoperative course was uncomplicated, and the patient has remained well during a 6 month followup period.

The segment of ileum and the duplication shared a common muscular wall, and the lumina were connected by a one mm wide orifice. The muscular wall of the duplication was thicker than that of the adjacent ileum, and its intraluminal surface exhibited prominent mucosal folds resembling a normal stomach (Fig. 5). Histologically, the enteric duplication was lined by normal-appearing gastric mucosa containing both fundal and antral gastric glands. No ulceration was found in the duplication or in the adjacent ileum.

Discussion

Evaluation of undiagnosed rectal bleeding still depends in large part on radiography of the gastrointestinal tract with intraluminal contrast media. A congenital lesion such as a Meckel's diverticulum or an enteric duplication is not readily demonstrated with these studies. However, the frequent presence of gastric mucosa within these

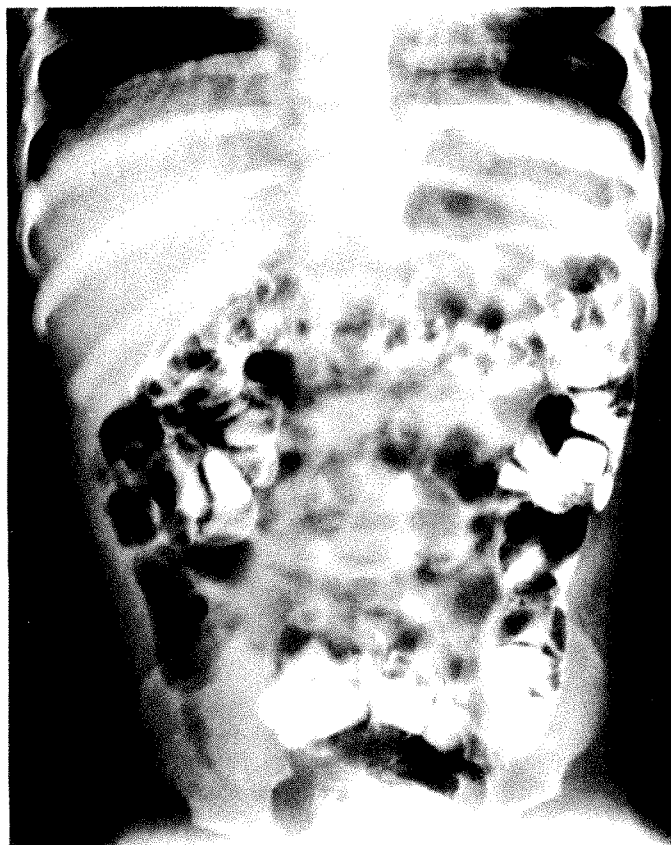


FIG. 1. Barium enema exhibiting extrinsic pressure on the cecum.



FIG. 2. Twenty-four hour delayed film revealing barium within a right lower quadrant lesion caudal to barium-filled cecum and appendix.

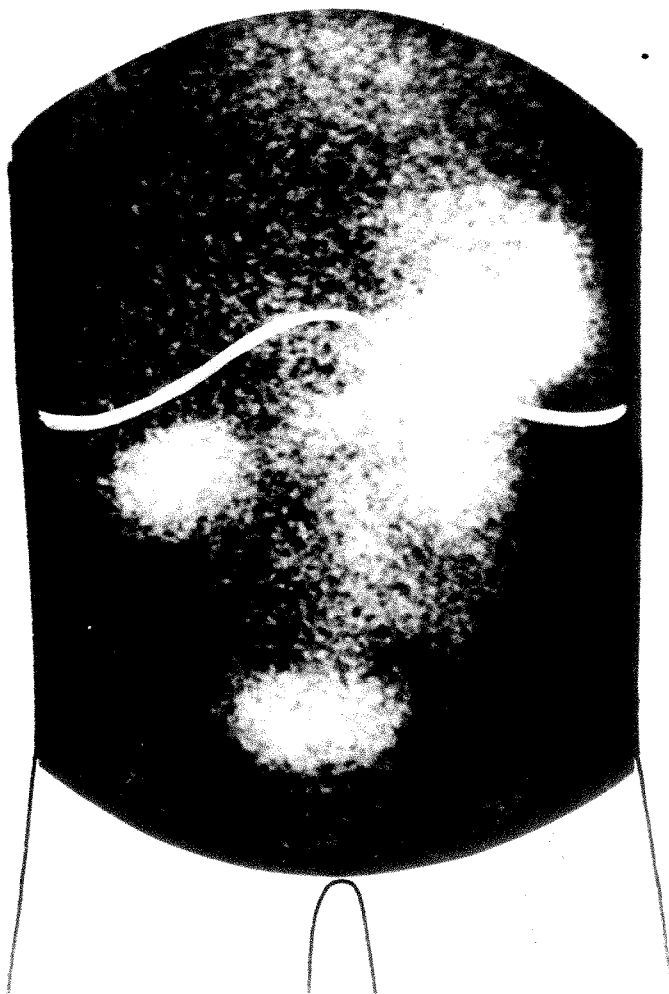


FIG. 3. ^{99m}Tc scan showing an area of increased activity in the right lower quadrant. Concentration of the pertechnetate ^{99m}Tc is also apparent in the stomach, small intestine, and bladder.

anomalies² makes their detection with pertechnetate ^{99m}Tc scanning possible.

This case is the first known report of positive pertechnetate ^{99m}Tc imaging in a patient with an intestinal dup-

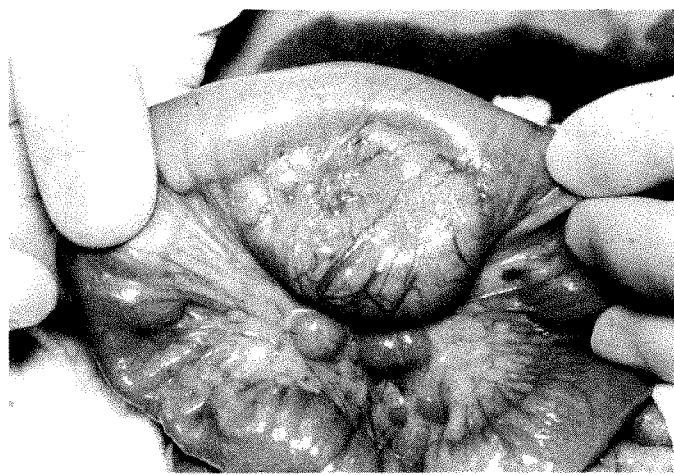


FIG. 4. Operative photograph illustrating the enteric duplication within the mesentery and attached to the intestine by a common wall.

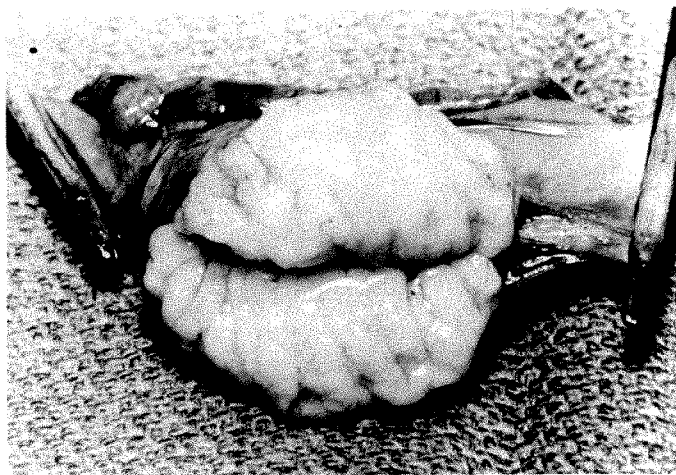


FIG. 5. Photograph of the resected specimen with the opened enteric duplication exhibiting a mucosal surface resembling that of a normal stomach.

lication. Further evidence is provided of the utility of the pertechnetate ^{99m}Tc scan as a safe, non-invasive diagnostic aid having application in the evaluation of gastrointestinal bleeding in infants and children. As this case illustrates, radionucleotide scanning may facilitate management by suggesting the appropriate diagnosis and localizing the anatomical lesion.

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Localization of Tissue Plasminogen Activator in Relation to Morphologic Changes in Human Saphenous Veins Used as Coronary Artery Bypass Autografts

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Employing the histochemical fibrin slide technique, we studied the localization of fibrinolytically active sites in relation to morphologic changes in saphenous veins used as coronary artery bypass autografts. Of veins from 100 patients undergoing surgery for coronary heart disease, 63 samples revealed well-demarcated intimal fibrinolytic activity. Distinct foci of lysis were present in the media and adventitia of all vein samples corresponding to the distribution of the vasa vasorum. Graft specimens obtained by autopsy from 13 patients surviving from 30 minutes to 13 days revealed considerable intimal damage with loss of fibrinolytic activity. Medial fibrinolytic activity disappeared early concomitant with disorganization of the medial muscle fibers, followed by necrosis, atrophy and fibrous transformation of the muscular structures. Adventitial activity disappeared later. One reoperation sample obtained after 8 weeks *in situ* showed moderate proliferative intimal fibrosis without an apparent neo-intima and without fibrinolytic activity, and one section showed evidence of valve cusp fibrosis, while most of the media had been replaced by fibrous tissue. Numerous foci of "medial"-adventitial fibrinolytic activity indicated presence of vascular structures in the venous wall. The fibrin slide technique is a convenient tool for studying the process of revascularization.

FOLLOWING THE WIDE ACCEPTANCE of the technique of the direct and immediate revascularization of the ischemic myocardium by saphenous vein autografts, introduced by Favaloro in 1967¹⁵ and extended by Johnson *et al.*,²² attention has focused on the structural changes which take place in the grafts. These changes are reported morphologically to resemble those occurring in grafts placed in peripheral positions. Intimal disruption and medial necrosis caused by wall ischemia are reported

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to characterize the early postoperative period.^{5,6,11,23,33,36,42} Later changes consist of intimal and subintimal fibrous proliferation^{3,5,10-12,17,18,20,21,23-25,28,29,32,36,39,40,42} while the histologic data on medial and adventitial fibrosis vary.^{3,16,17,25,28,29}

The intima of human veins usually exhibits fibrinolytic activity caused by a plasminogen activator present in the endothelial cells.^{2,9,38} In contrast, the human arterial intima commonly is inactive or only weakly active. Fibrinolytically active sites in media or adventitia are related to the vasa vasorum.

The present study, covering mainly the early postoperative period, is an attempt to correlate possible changes in the fibrinolytic activity of the richly vascularized veins with the sequences of events occurring in response to surgical trauma, severance of adventitial blood supply and transfer to the arterial system. Presence of fibrinolytic sites in the external layers of the transplanted veins indicate whether revascularization has occurred.

Materials and Methods

Vein Samples

Specimens were collected from patients at the Massachusetts General Hospital, Boston. At operation the 8 to 10 inch segment of the long saphenous vein was flushed with saline containing heparin, wrapped in a saline-moistened towel and kept at room temperature until used as a reversed graft one to two hours later. Remaining vein pieces were placed in small, sterile,

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FIG. 1. Normal saphenous vein (A-sample) showing typical pattern of distribution of medial-adventitial fibrinolytic activity on fibrin slides after 15 minutes of incubation. Magnification ($\times 36$).

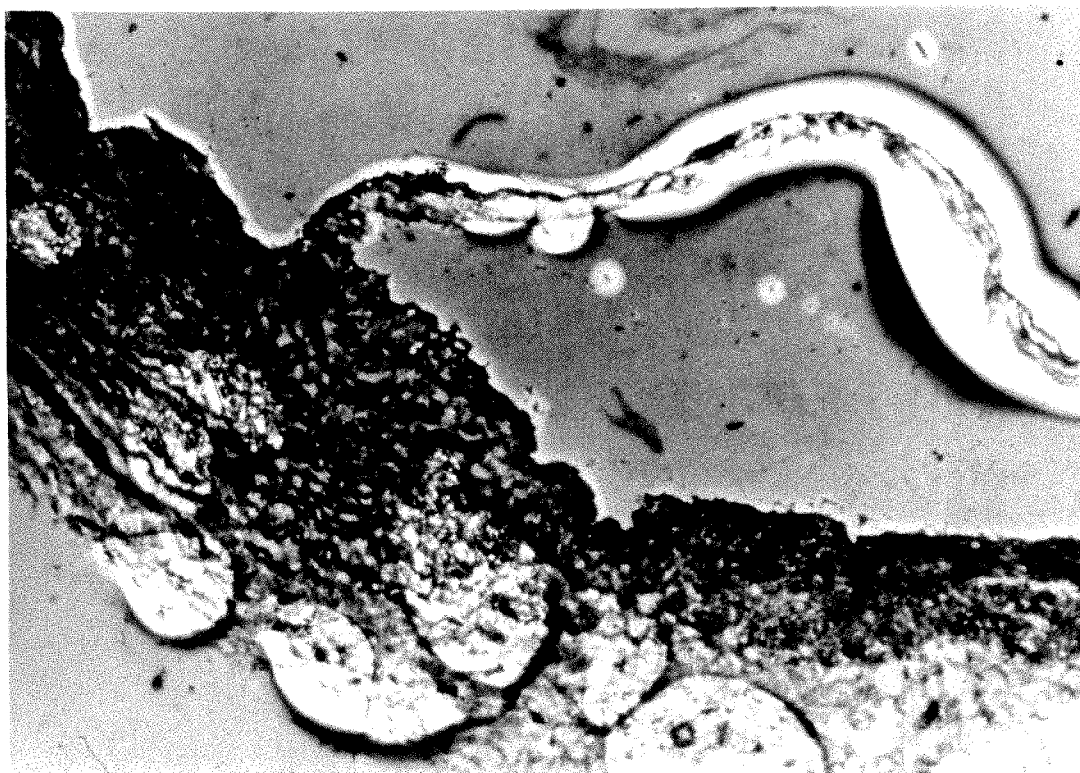
stoppered glass vials and kept at -20°C until shipped in dry ice for investigation. Storage of sealed specimens of vessels for several weeks, or even months, at -20°C was found not to influence their fibrinolytic activity. Specimens

from a total of 100 patients were studied (A-samples). Subsequently, if surgical re-exploration or autopsy provided the opportunity, the grafted vein was removed, the usually adherent clot was washed away,



FIG. 2. Normal saphenous vein showing well-demarcated fibrinolytic activity along an apparently intact endothelium. Incubated 30 minutes; Magnification ($\times 36$).

FIG. 3. Normal saphenous vein cut at valve level. Intense fibrinolytic activity along lining of valve after 20 minutes of incubation. Magnification ($\times 38$).



and the specimen, wrapped in aluminum foil, was placed in a stoppered vial and immediately stored at -20°C . Such specimens will be called B-samples. Of 14 B-samples received, only one was obtained by reoperation.

Histochemical Procedures

Frozen sections, $6-8\ \mu$ thick, were collected on pre-cleaned microscope slides and dried in the air for a few minutes. Cross sections were cut from each specimen at as many levels as possible. At least one longitudinal section was also made. The localization of sites with fibrinolytic activity was determined by the histochemical fibrin slide technique of Todd³⁸ as modified.²⁷ Briefly described, the procedure was as follows: Volumes of 10 microliter of bovine thrombin solution, 20 NIH units per ml in saline and 60 microliter of an 0.7% solution of bovine, plasminogen-rich fibrinogen in phosphate buffer at pH 7.75 and $I=0.15$, were applied to each prepared slide, mixed, and evenly spread over an area of 2.5×4 cm. After clot stabilization for 15-20 minutes in a moist chamber kept at $10-15^{\circ}\text{C}$, slides were incubated at 37°C for 5, 10, 20, 30, 45 and 60 minutes. After fixation in 10% formaldehyde the slides were rinsed in tap water, stained in Harris' alum hematoxylin and mounted in glycerin jelly. The localization of fibrinolytic sites, appearing as pale areas of lysis in the bluestained fibrin, can be correlated with the morphological structures of the tissue sec-

tions. Tests for unspecific, neutral protease activity were made with fibrin films prepared with plasminogen-free fibrinogen and incubated for 60 minutes. For general histological examination parallel sections were stained with Mayer's hematoxylin and eosin and after van Gieson. Frozen sections from most of the B-samples were also stained for fibrin after Mallory.

Results

None of our specimens produced lysis of fibrin films prepared with plasminogen-free fibrinogen. The absence of neutral protease activity indicated that fibrinolysis in all instances was caused by a plasminogen activator.

A-samples: Medial-adventitial Activity

All one hundred specimens showed the same topography of fibrinolytic sites in the media and adventitia. Distinct foci of lysis, appearing after incubation for 10-20 minutes, were associated with the vasa vasorum of the richly vascularized saphenous vein, reaching into the middle circular layer of its tunica media (Fig. 1).

Intimal Activity

Intimal fibrinolysis occurred in 63 specimens after incubation for 30-45 minutes (Fig. 2). There was no intimal fibrinolytic activity in the remaining 37 specimens after incubation for 60 minutes. Thereafter, the intensive medial-adventitial activity precluded evaluation. Intima-

TABLE 1. *Samples of Venous Grafts (B-Samples)*

Pt. No.	Survival Time	Fibrinolytic Activity* and Structural Changes	
		B-Samples	A-Samples**
105	In situ for about 30 min	Branch level. No intimal or medial activity. Considerable adventitial activity after 60 min restricted to branch side. Fibrin reaction along luminal lining. Fragment of clot in lumen. Structure preserved.	(Missing)
8	Expired same day	No intimal or medial activity. A few foci of adventitial activity after 30-45 min. Structure preserved.	After 30 min, scattered.
15	Expired same day (5 hrs)	Scattered activity after 45-60 min. along disrupted intima. No medial activity. A few foci of adventitial activity after 60 min. Structure preserved.	(Missing)
63	Expired same day	Intimal activity after 35-60 min. at cellular dislocations. Medial-adventitial activity after 30-45 min. Structure preserved.	After 20 min, small, patchy focal zones of lysis.
65	Expired same day	Patchy focal activity after 60 min along disrupted intima. No medial activity. A few foci of adventitial activity.	(Missing)
72A	Expired same day	No intimal activity. Moderate medial-adventitial activity after 45-60 min. Structure preserved.	No intimal activity (also absent at branch site).
73A	1 day	Scattered intimal activity after 30-60 min. At branch level intense activity already after 20 min. A few foci of medial activity. Pronounced adventitial activity after 30-45 min. Structure preserved.	After 45-60 min; after 20 min at valve level.
71A	2 days	Branch level. After 45 min patchy focal activity along disrupted intima. Very few foci in adventitia after 60 min. Thin-walled, structure not preserved.	No intimal activity
26	2½ days	Weak intimal activity related to detached cells. Very few foci in media-adventitia after 45-60 min. Fibrin reaction in adventitia. Fragment of clot in lumen. Disorganization and decrease in number of muscular elements in media.	After 45 min, scattered; after 10 min at valve level; after 20 min in branch.
27	4½ days	No intimal activity. Some medial activity in relation to remaining muscle fibers after 45-60 min. A few active foci in adventitia. Fibrin reaction along luminal lining and in adventitia. Decrease in number of smooth muscle fibers in middle circular layer. Decrease in thickness of wall. Architecture still recognizable.	After 45 min, scattered, weak, mainly at cellular dislocations. After 20 min at branch site.
94A	8 days	After 60 min scattered intimal activity at a few sites of cellular dislocation. No medial-adventitial activity. Fibrin reaction on luminal side and in thickened adventitia. Some vasa occluded by thrombi. Fragment of clot in lumen.	(Missing)
7	9 days	No intimal or medial activity. Fragment of clot in lumen. Strong fibrin reaction in thickened adventitia. Necrotic appearance with loss of most muscular elements. Decrease in thickness of wall.	(Missing)
64	13 days	No intimal activity. A few foci of "medial"-adventitial activity, after 30-45 min close to preserved muscle fibers, suggesting partial revascularization.	No intimal activity
41	Reoperation.	Innermost inactive layer consisting of moderately proliferating fibrous tissue. In some sections a fibrous plaque protruded into lumen. Loss of wall structure with most muscular elements replaced with fibrous tissue. Decrease in wall thickness. Numerous foci of "medial"-adventitial activity after 20-30 min indicating revascularization.	(Missing)

*Time periods refer to length of incubation of fibrin slides.

**Refers only to the intimal activity. The medial-adventitial activity and the architecture of A-samples showed a constant pattern (see text).

related fibrinolytic activity was considerably higher at branch or valve levels. Figure 3 presents a section cut at the level of a venous valve. After 20 minutes of incubation particularly high intensity of lysis is evident along the lining of the valve.

B-samples

The data for the grafted veins and their corresponding A-samples are summarized in Table 1. In five instances the A-sample is missing. The patient survival time varied from a few hours to 13 days. In one patient (#105) the graft was *in situ* for only 30 minutes. All B-samples were frail and difficult to cut. Specimens obtained before the second postoperative day retained most of their original architecture. Two days postoperatively, disorganization of muscle fibers in the tunica media became apparent. In the older specimens necrosis and atrophy had progressed and most of the muscular structures had been replaced by fibrous tissue. There was considerable disruption and loss of endothelial lining in all specimens, including those of the very early postoperative period. The disrupted endothelium and some desquamated endothelial cells (7 specimens) showed fibrinolytic activity after incubation for 45-60 minutes. The marked decrease or complete disappearance of medial fibrinolytic activity, even in specimens with well-preserved morphology, was a most striking finding. Adventitial activity (except for sample #73A) was likewise diminished and was absent from the eight postoperative day. Some Mallory-stained sections showed a reaction for fibrin along the damaged intima and in the damaged adventitia. Clot fragments were observed in the lumen of three samples.

Figure 4 shows a section from a graft *in situ* for only 30 minutes. This particular section was cut at the level of a small branch. A diffuse layering of thin fibrinous material (clearly visible in Mallory stained sections) involves most of the inactive luminal lining with a clot fragment at one site. There was no trace of medial fibrinolytic activity even after prolonged incubation. Zones of marked adventitial activity, appearing after 60 minutes of incubation, are limited to the perivascular connective tissue surrounding the branch, a site normally exhibiting intense fibrinolytic activity. The appearance of a 4½ days old graft is shown in Figs. 5a-d (Pt. #27). The sections in Figs. 5a and b are from the corresponding A-sample after 10 and 45 minutes of incubation, respectively. Two sections from the B-sample, cut at different levels, are shown in Figs. 5c and d after incubation for 60 minutes. When Fig. 5c is compared with Figs. 5a and b it is obvious that a marked decrease has occurred in the medial-adventitial fibrinolytic activity coincidently with the morphological disorganization resulting in separation and loss of smooth muscle fibers. Figure 5d is a section from the level of a venous valve where thrombotic mate-

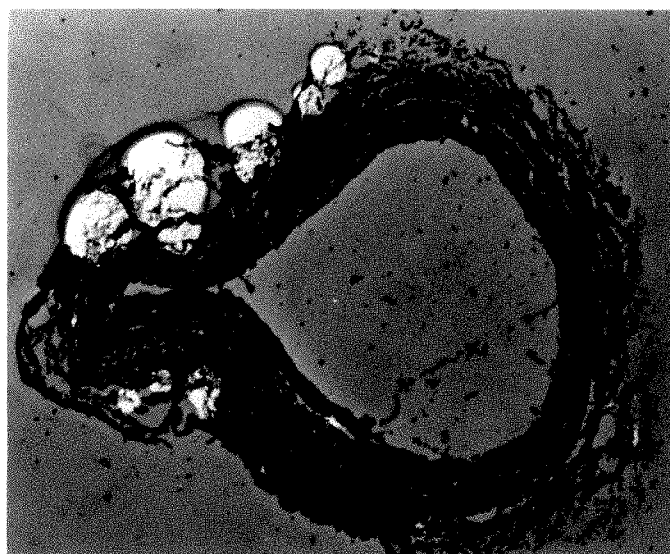
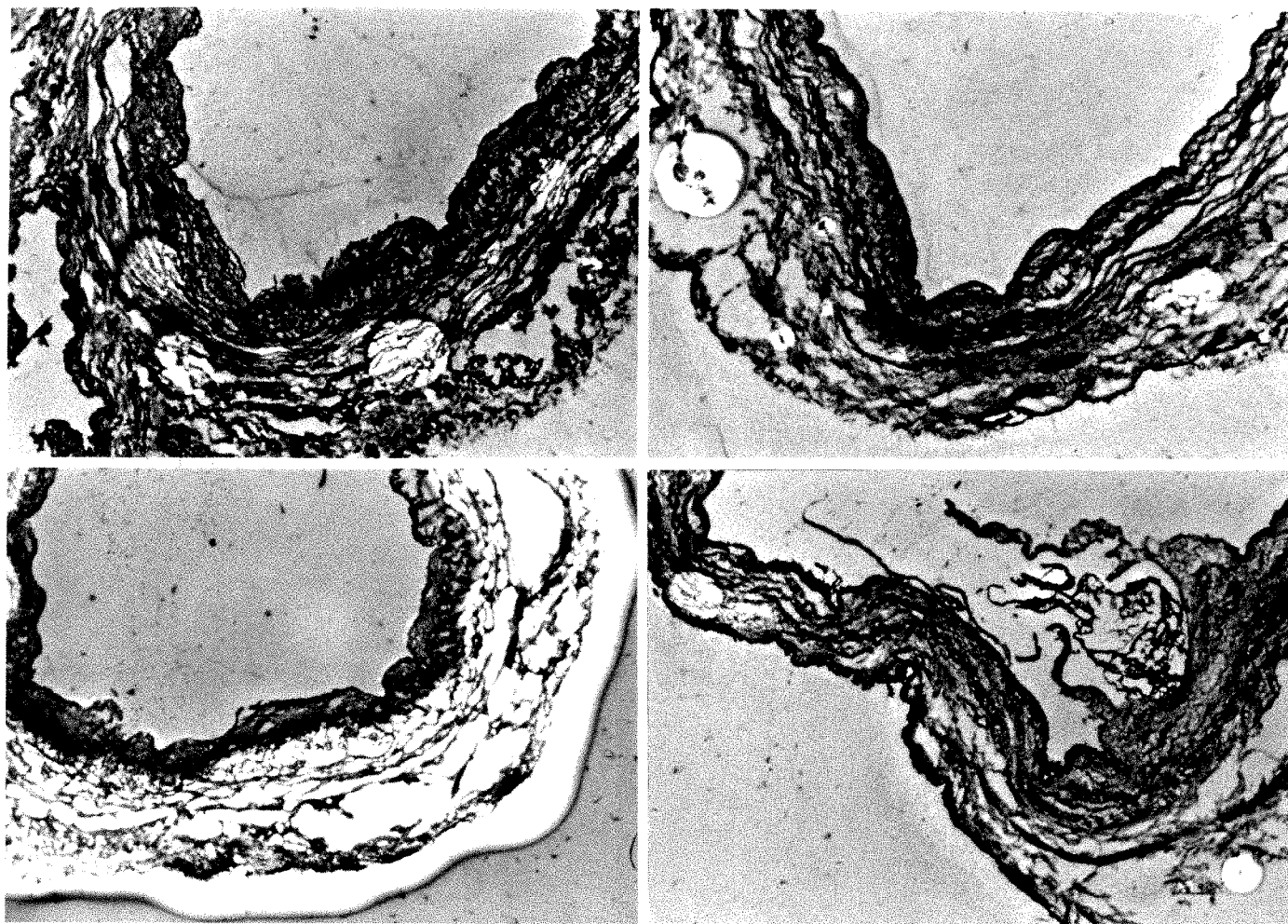


FIG. 4. Graft sample (B-sample) from Pt. #105 whose graft had been *in situ* for about 30 minutes. The specimen was cut at branch level. A diffuse layering of thin fibrous material involves most of the fibrinolytically inactive lumen, with a clot fragment at one site. No medial activity. Pronounced adventitial activity is limited to the perivascular tissue of the branch site. Magnification ($\times 15$).

rial with weak fibrinolytic activity is seen in the valve pocket. Not a trace remains of the extremely high fibrinolytic activity which we usually found related to the endothelium of an undamaged venous valve (Fig. 3). A section from a patient (#94) surviving for 8 days is shown in Fig. 6. This is the only specimen in our series which shows a definite thickening of the venous wall. The increase in thickness is mainly due to a fibrous and Mallory-positive adventitia with interspersed longitudinal muscle fibers and some occluded vasa. Muscle fibers in the outer layer of the media are separated by fibroblastic proliferation. A positive fibrin reaction was seen along the entire luminal side with a fragment of a protruding clot attached at one site. Fibrinolytic activity was absent even in sections incubated for 60 minutes. Figure 7 shows specimens from a patient (Pt. #64) surviving for 13 days. The A-sample (Fig. 7a) was incubated for 20 minutes. The B-sample (Fig. 7b) was incubated for 60 minutes. While most of the venous wall was necrotic and devoid of fibrinolytic activity, some areas adjacent to sites of adventitial fibrinolytic activity have preserved part of their normal morphology. Apparently, their location is limited to areas where adventitial revascularization is taking place. A focal, plaque-like fibrous intimal thickening is seen related to the revascularized area.

The reoperation sample was from a graft which became occluded after 8 weeks (Pt#41). Figures 8a and b show sections incubated for 20 minutes. The innermost layer appears to consist of moderately proliferating fibrous tissue without an apparent neointimal lining and without fibrinolytic activity even after prolonged incubation. The



FIGS. 5a-d. Fibrinolytic patterns of samples from Pt. #27. The A-samples are shown in Fig. 5a (top left) (10 min. of incubation) and Fig. 5b (bottom left) (45 min. of incubation). Medial and adventitial activity became confluent with prolonged incubation. Weak endothelial activity related to an area of dislocation. The B-samples (obtained 4½ days postoperatively) are shown in Figs. 5c and d after 60 minutes of incubation. Figure 5c (top right) shows marked decrease in medial-adventitial activity coincidentally with disorganization and decrease in number of smooth muscle fibers. The section in Fig. 5d (bottom right) is cut at the level of a venous valve. Thrombotic material with some fibrinolytic activity is seen in the valve pocket. The lining of the damaged valve is inactive. Magnification ($\times 19$).

original structure is hardly recognizable as most of the muscular elements of the media have been replaced by fibrous tissue. There is also a decrease in the overall thickness of the venous wall. Numerous foci of "medial"-adventitial activity suggest a process of revascularization (Fig. 8a). Unfortunately, only a very small segment of this sample was available for investigation, so that sectioning at only two levels was possible. Sections cut at the other level show foci of adventitial activity adjacent to a fibrous plaque of considerable size protruding into the lumen and suggesting valve cusp fibrosis (Fig. 8b).

Discussion

Normal Samples (A-samples)

Characteristically, the specimens of saphenous veins used for grafting showed a well-demarcated intimal fibrinolytic activity in 63 of the 100 specimens after incuba-

tion of the frozen sections on fibrin slides for 30-45 minutes. All the specimens showed marked medial-adventitial fibrinolysis, often producing foci of lysis after incubation for only 10-20 minutes. They followed the distribution of the vasa vasorum and particular intense lysis was related to zones in the middle circular layer. Pandolfi *et al.*,³⁵ studying biopsy samples of the great saphenous vein from 23 patients operated on for varicose veins, found the fibrinolytic activity mainly related to the vasa vasorum of the adventitia, while the media contained a varying number of only moderately active vessels. This discrepancy in results might be related to differences between the two groups of patients studied.

The absence of intimal fibrinolytic activity in many of our A-samples may result from damage to the delicate endothelium caused by handling of the specimen or by the flushing with saline prior to grafting. Wyatt and

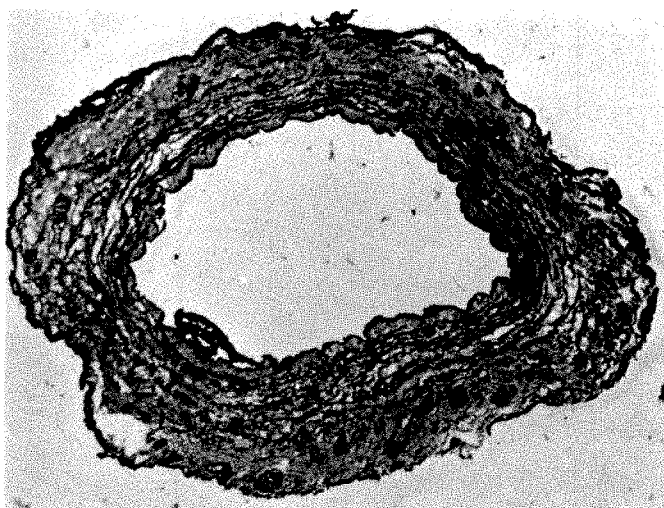


FIG. 6. B-sample from Pt. #94 who survived for 8 days. The entire venous wall is thickened. This is mainly due to the fibrous and Mallory-positive adventitia with interspersed smooth muscle fibers and some occluded vasa. Muscle fibers in the outer layer of the media are separated by fibroblastic proliferation. A protruding clot is attached to one site of the lumen. The entire section is devoid of fibrinolytic activity. Incubated 60 minutes. Magnification ($\times 18$).

Taylor,⁴² studying the endothelium of vein grafts inserted into the femoral artery of dogs, found the endothelium normal after perfusion *in situ* with saline for 90 minutes. However, when the vein specimens were dissected and soaked in saline, only 40-50% of them had retained an endothelial lining and many endothelial cells had broken outlines (silver stain). The authors correlated their observations with the findings of Zweifach⁴³ that mechanical stimulation of veins *in vivo* produces endothelial desquamation. Johnson²¹ attributed a late complication of sporadic subintimal fibrous proliferation in the graft in part to the local damage done at the time of surgery. He suggested that the vein be left *in situ* until the last minute before removal for grafting.

While it is difficult to explain the absence of intima-related activity in A-samples which otherwise present an apparently histologically normal endothelial lining, it should be kept in mind that examination of the endothelium in cross sections by light microscopy is difficult. Thus, Brody *et al.*⁶ observed ultrastructural alterations in the endothelium of dog cephalic and femoral veins isolated by surgery and flushed with a saline-heparin solution, although the veins appeared normal by light microscopy. Interpretation of frozen sections is also limited by the distortion occurring during their preparation. Several authors have suggested that plasminogen activator may escape from endothelial cells to appear in the bloodstream. Thus, Clarke *et al.*⁸ found increased fibrinolytic activity in blood following venous occlusion, an observation subsequently confirmed by several authors. Chakrabarti *et al.*⁷ reported an increased fibrinolytic activity in blood drawn from veins which had been

traumatized by pinching with dissecting forceps, and nonfibrinolytic, citrated plasma placed for 2 minutes in a clamped segment of the saphenous vein *in situ* became fibrinolytic. Aoki and von Kaulla¹ prepared large quantities of plasminogen activator by post-mortem flushing of the vascular tree with saline. Hence, it appears that endothelial cells easily release their fibrinolytic activity. Because all our specimens were from arteriosclerotic patients, they might not be representative for a population without vascular disease. Thus, Pandolfi *et al.*³⁴ and Isacson and Nilsson¹⁹ reported that the rise in blood fibrinolytic activity usually following venous occlusion was absent in patients suffering from recurrent venous thrombosis and they related this observation to a lower content of plasminogen activator in the venous walls of these patients.

Graft Samples (B-samples)

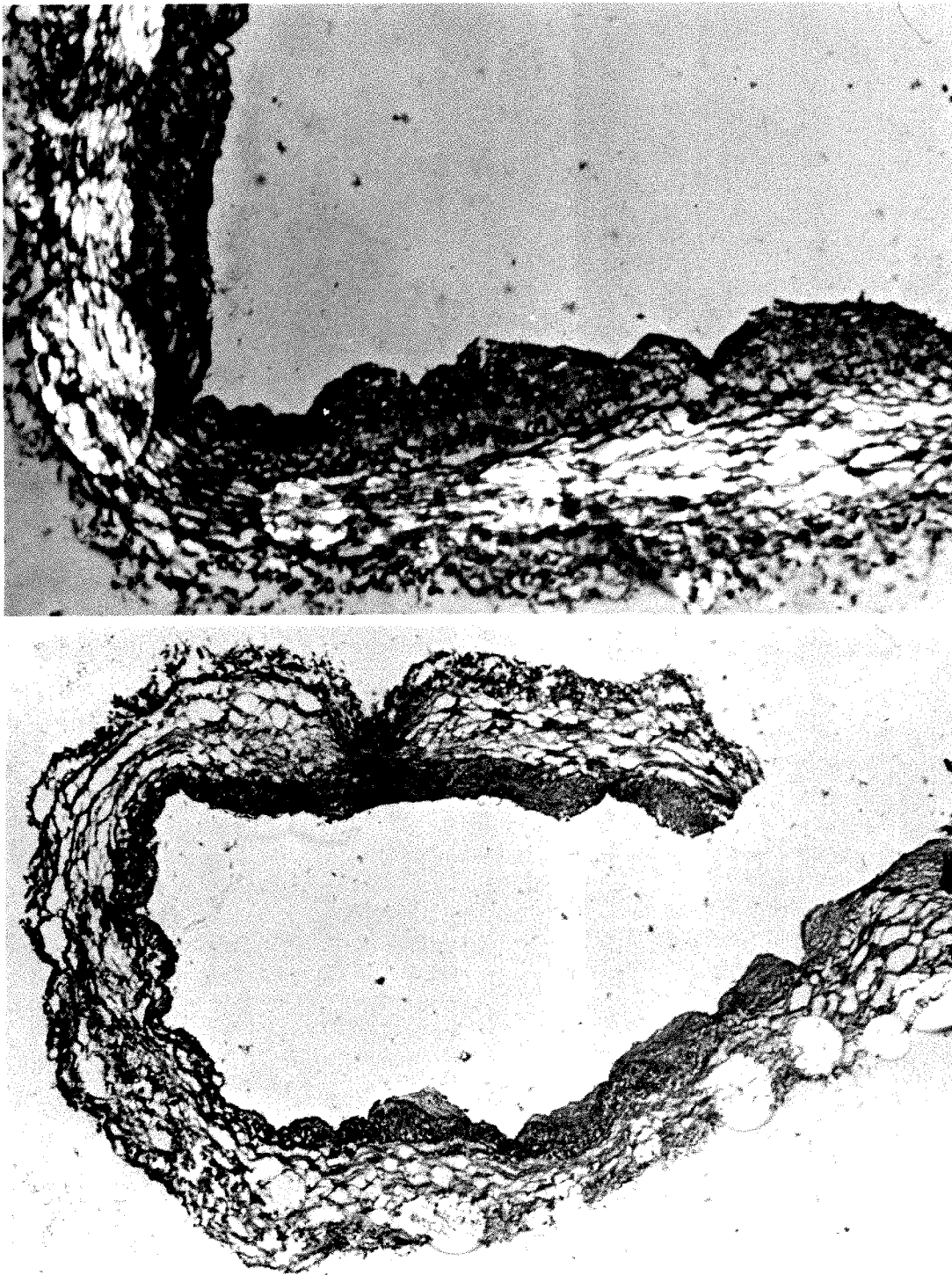
Because of the small number of our B-samples and the patient's short survival times, our findings may not be representative for the group as a whole. The autopsy specimens were from early failures caused by thrombosis. Thrombosis most likely occurs within the first few weeks following operation while grafts which remain angiographically patent 3 to 6 months after surgery are not known to thrombose.¹⁴ Despite these limitations, our observations contribute to the description of postoperative changes in vein grafts.

1. Early Changes

Loss of Endothelium. The regularly observed denudation of the intima most likely is caused by surgical damage, by the unaccustomed arterial pressure, or by metabolic disturbances following severance of the adventitial blood supply. DeWeese *et al.*¹¹ found femoropopliteal bypass grafts to undergo an early loss of endothelium followed by the development of an inner layer composed of fibroblasts and collagen. Likewise, Wyatt and Taylor⁴² found only about 30% of the inner surface of early vein grafts, inserted in the femoral artery of dogs to consist of endothelium, the denuded surface being cov-

described focal endothelial disruption with fibrin deposition in canine femoral grafts, and endothelial damage and loss were reported to be characteristic histologic changes in the early postoperative period in aorta-coronary bypass grafts in dogs.^{5,36} O'Neill³³ studying the circulation in the canine vein wall observed desquamation of the endothelium as a sequel to the deprived blood supply. Obviously, the above-mentioned reports offer sufficient explanation for the marked loss of intima-related fibrinolytic activity in our B-samples.

Medial Necrosis Due to Wall Ischemia. Another conspicuous lesion in our autopsy material is the necrosis of the myocytes which leads to medial disorganization with

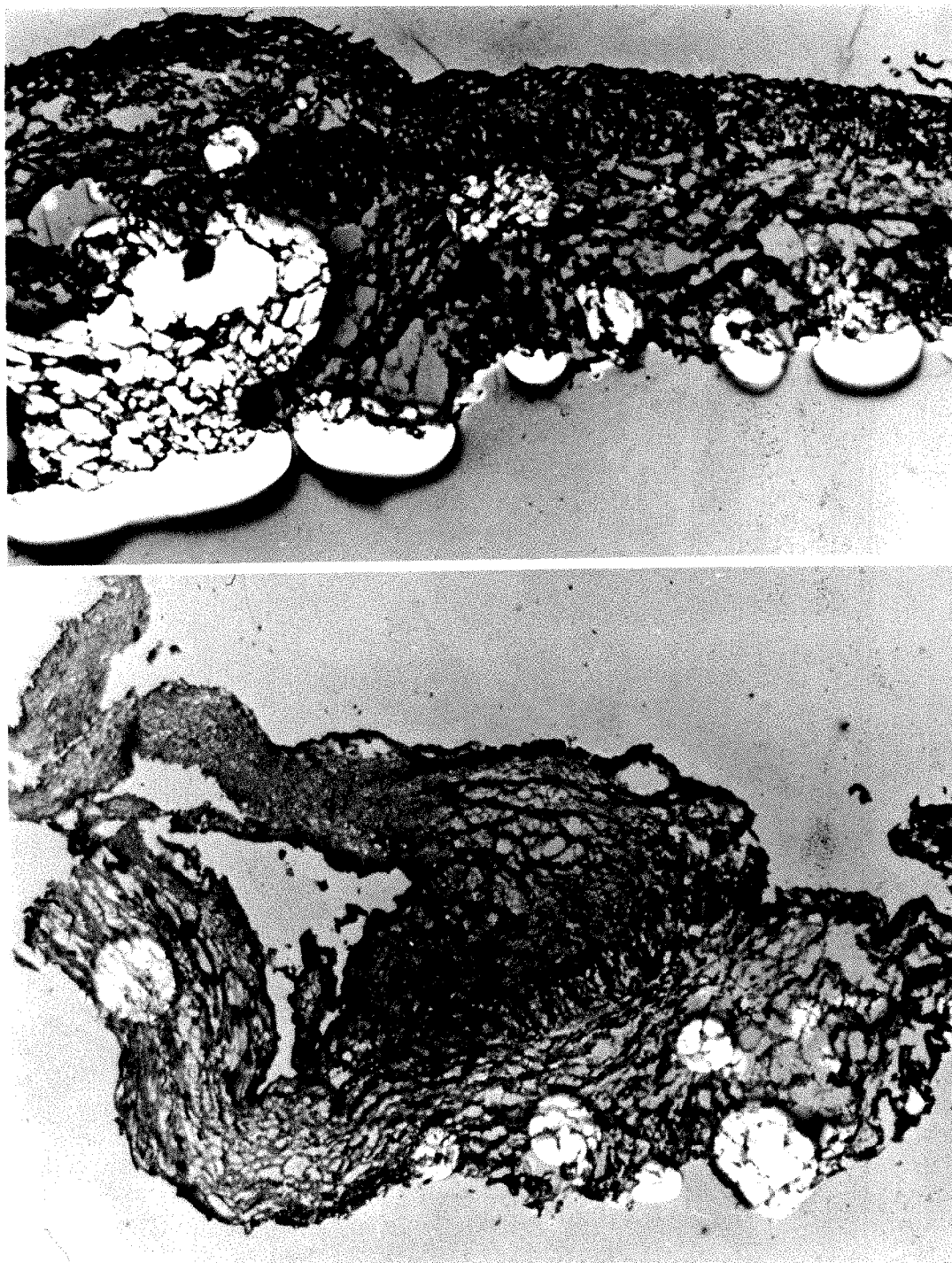


FIGS. 7a and b. Samples from Pt. #64. (top) The A-sample showed after 20 minutes of incubation the typical distribution of medial-adventitial activity. Magnification ($\times 30$). The B-sample (bottom) (obtained 13 days postoperatively) is shown in Fig. 7b. The wall is mostly necrotic except for an area where a few active vessels are seen in the adventitia after 60 minutes of incubation. A focal, plaque-like, intimal thickening with preservation of some of the histologic structure in the inner media is limited to this area. Magnification ($\times 15$).

loss of muscular elements in association with various degrees of mural fibrosis. In samples obtained 9 (Pt. #7) and 13 days postoperatively (Pt #64, Fig. 7b) the entire venous wall appeared necrotic, except for a small part of sample #64 where the original structure was partially preserved in close association with the apparently restored and fibrinolytically active vasa vasorum. Obvious-

ly, some ischemic medial muscle cells do recover following revascularization. Postmortem autolysis as a cause of necrosis has never been encountered in immediately frozen samples of vessels obtained by necropsy either by Todd or by ourselves. Necrosis and loss of muscular elements increased with the time the graft had been in place. Furthermore, autolysis is not consistent with the

FIGS. 8a and b. B-samples from Pt. #41 whose graft became occluded after 8 weeks. In Fig. 8a the innermost layer appears to consist of moderately proliferating fibrous tissue apparently without a neo-intimal lining and without fibrinolytic activity. Most of the muscular elements have been replaced with fibrous tissue. Numerous foci of "medial"-adventitial activity suggest revascularization ($\times 37$). Incubated 20 minutes. Fig. 8b shows a fibrous plaque of considerable size protruding into the lumen and presumably representing valve cusp fibrosis. Incubated 20 min. ($\times 34$).



thickening of the wall of the 8 day old graft in Fig. 6. Likewise, the appearances of the revascularized area of the autopsy sample obtained 13 days postoperatively (Fig. 7b) and that of the re-operation sample functioning for 2 months (Fig. 8a) are strikingly similar.

Our findings in specimens from the early postoperative period substantiate those of DeWeese *et al.*¹¹ who reported early necrosis in thrombosed femoropopliteal

bypass grafts with subsequent regeneration of medial muscle cells following revascularization after a week or more. Extensive medial necrosis in the early postoperative period followed by fibrosis was also described by Jones *et al.*,²³ Silver *et al.*,³⁶ and Brody *et al.*,⁶ the latter two reporting on canine coronary artery bypass grafts. Brody *et al.*⁶ emphasized the close similarity of graft alterations in dog and man. McCabe *et al.*²⁹ reported on

changes in the medical coat of canine and human saphenous veins used in experimental and clinical peripheral arterial reconstruction. In addition to an acute inflammatory exudate causing marked thickness of the media, inflammatory cells were seen lying in a network of fibrin in the adventitia. The strong fibrin reaction in the thickened adventitia and in the outer media in some of our samples suggests a similar initial inflammatory response, although we did not observe cellular infiltration. McCabe *et al.*²⁹ also observed an apparent loss of smooth muscle fibers after 4 weeks concomitant with deposition of collagen and medial thickening. Enclosure of the grafts in nylon to prevent revascularization greatly increased the loss of smooth muscle cells and the venous wall became much thicker.

Revascularization. Obviously, revascularization depends upon anastomosis of the vasa of the adventitia of the transplant with surrounding vascular structures, and the formation of a granulation tissue which unites the graft with its bed. Our limited material did not allow us to systematically follow the process of revascularization. Only one sample in our autopsy material presents evidence of re-establishment of the adventitial blood supply (Fig. 7b, 13 days postoperatively). The reoperation sample (Figs. 8a and b) which remained *in situ* for 2 months, is another example of revascularization, although structural disorganization and medial fibrosis were marked and the graft finally failed. Nevertheless, the fibrinolytically active vascular structures localized in these specimens showed that the fibrin slide technique is a convenient tool for the study of revascularization. The technique also demonstrated a surprisingly early disappearance of medial fibrinolytic activity. This may indicate great vulnerability and early degeneration of the endothelium of the medial vasa in response to a disparity between nutritional requirements and nutritional supply prior to re-establishment of the circulation in the venous wall.

Several investigators have studied the process of revascularization. Employing an india ink technique, Wyatt *et al.*⁴¹ presented evidence of the establishment of a circulation in the wall of canine saphenous veins bypassing the femoral artery, as early as 72 hours following grafting. However, it took 2 months before an almost normal pattern of vascularization had developed. McCune *et al.*,³⁰ tracing the reconstruction of the vasa vasorum in canine aortic homografts with india ink, found many blood vessels in the graft wall one week after implantation. After 3-6 months they extended throughout the adventitia and into the outer third of the media. Sugiura,³⁷ who studied autogenous canine femoral veins grafted into femoral arteries by microangiography, also found the establishment of the vasa vasorum to begin within one week and to be complete 2-3 months after

operation. Nakata³² studying vascular lesions following experimental obstruction of the vasa vasorum of the abdominal aorta in dogs, observed vessels 2-3 weeks postoperatively. Kiehn *et al.*,²⁶ using radioactive phosphorus as an indicator of the revascularization of canine autogenous and homologous arterial grafts, found the isotope uptake to be significantly lower in early grafts (5 or 10 days) than in older grafts (30 days).

2. Late Changes

So far, the observed histologic changes of autogenous venous grafts used for coronary artery bypass are similar to those described in peripheral arterial reconstructions with intimal and subintimal proliferation being the dominant feature in patients^{3,15,17,20,21,22,25,28,39,40} as well as in animals.^{5,36} The intimal lesions consist of young connective tissue without fat suggesting proliferative repair of the damaged endothelium. Johnson,²¹ in particular, emphasized the possible technical cause of these proliferative lesions and stressed the importance of a gentle and careful manipulation of the delicate saphenous veins. The absence of a significant degree of intimal fibrosis in our autopsy samples can be explained by the short survival time. The focal, plaque-like moderate thickening in Fig. 7a occurring in a revascularized area of an otherwise necrotic vein, may indicate an early stage of intimal proliferation. There was moderate fibrous proliferation in the reoperation sample obtained after 8 weeks (Fig. 8a). A section of the same sample cut at a different level shows, however, a fibrous plaque of considerable size protruding into the lumen and suggesting valve cusp fibrosis (Fig. 8b). The extremely high fibrinolytic activity which we usually found to be present along the lining of venous valves apparently had disappeared so that no local fibrinolytic activity was available for prevention of thrombosis in the valve pocket (Fig. 5d). Several authors have reported on segmental stenosis due to valve cusp fibrosis^{3,4,12,13,16,31} and DeWeese *et al.*¹¹ suggested rupture of competent valves to avoid stenosis.

An experimental study of fibrinolytic activity in dog vein grafts in relation to the development of intimal fibrous proliferation, the gradual transformation of the media into collagenous tissue, and the progress of revascularization, is in progress.

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A New Variant of Intra-abdominal Hernia

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A new variant of intra-abdominal hernia is presented. Available evidence suggests that this type of intra-abdominal hernia may be more prevalent than previously reported. Patients suffering from crampy, intermittent abdominal pain whose routine radiographic gastrointestinal studies are unrevealing often are labeled as having psychogenic disorders. Three cases are presented giving similar histories and routine findings in which mesenteric arteriography coupled with careful small bowel series has revealed a surgically curable lesion. Such patients should have judicious mesenteric angiography coupled with routine radiographic gastrointestinal studies in search of small intramesenteric herniae which are readily correctible.

ALTHOUGH internal herniae have been described since 1742, and have been known as a definite clinical entity since 1857, the number of case reports remains quite small. The reported cases number only in the hundreds although the actual incidence most certainly is much greater.^{4,6,7,10} Identification either preoperatively or at surgery is difficult. Large paraduodenal herniae may be readily seen by upper gastrointestinal series. However, at the time of surgery small paracecal, intrasigmoidal, or other small internal herniae can be readily missed. In the course of laparotomy and inspection of the small bowel, these herniae may well be reduced and go unrecognized.

Internal herniae may be either developmental or acquired. The herniae due to developmental, rotational anomalies may be more uncommon than those of the acquired type, which may be idiopathic, secondary to surgery, inflammation or trauma. An excellent review of the embryology associated with rotational anomalies has

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been presented by Zimmerman and Kaufman,¹⁴ who feel that although any incarceration in the abdominal cavity may be called an internal hernia, to do so may be confusing. It is now possible to diagnose intra-abdominal symptomatic herniae which may truly be classified as internal with new and sophisticated radiologic techniques. McKail⁸ in 1961 described certain intra-abdominal herniae as typically presenting as an acute abdominal emergency leading to strangulation and death if not relieved. In contrast to this clinical situation, we have found that we are able to preoperatively diagnose a previously undescribed variant of intra-mesenteric internal hernia by means of visceral angiography. These may be repaired electively with excellent results. In these cases, none presented as severe acute abdominal emergencies but rather as chronic, vague, unexplained recurrent abdominal pain. The usual barium studies showed equivocal small internal herniae containing small bowel, but superimposed angiography definitely outlined the abnormality in each case which was subsequently proven at surgery. In the first case in this series the hernia was reduced during the course of running the small bowel and thus went unrecognized by the surgeon except in retrospect. The subsequent two cases had the herniae readily identified at surgery as rents in the mesentery in exactly the area predicted by preoperative selective visceral arteriograms.

Case Reports

Case 1: V.P., a 38-year-old Puerto Rican male, was admitted in March, 1972, for evaluation of lower abdominal pain of 8 weeks duration. This was unrelated to food intake. The pain was episodic and to the right of the midline. He experienced occasional nausea but no

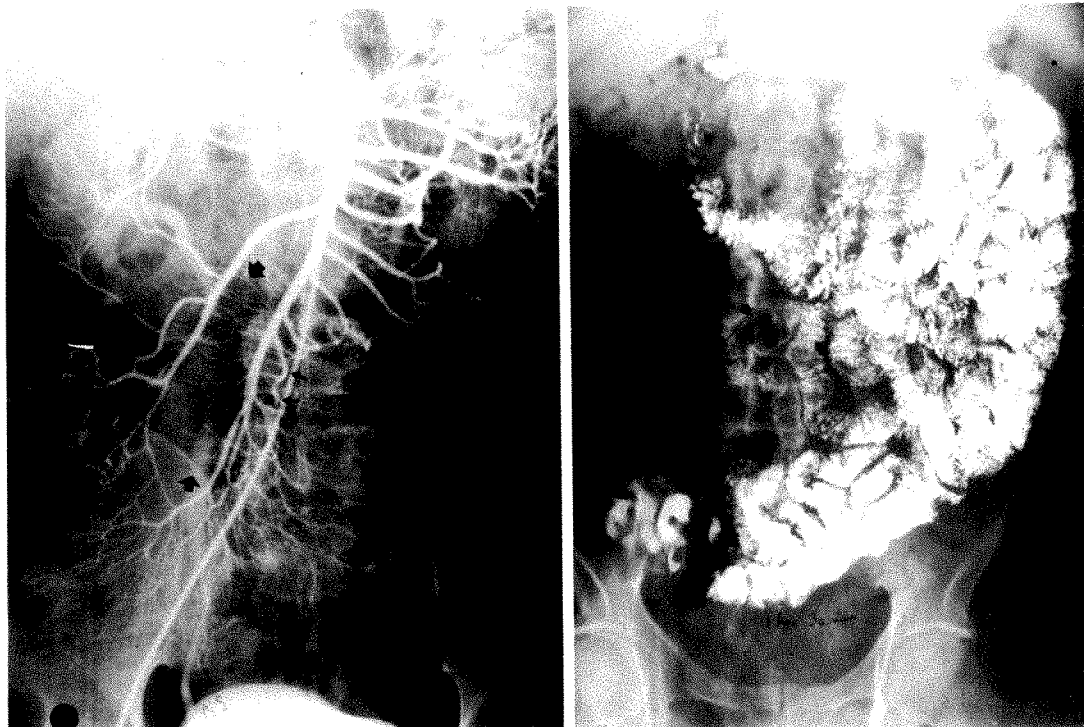
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FIGS. 1a and b. (left) Angiography of Case 1 revealing the crossing of jejunal branches to the right of SMA axis between the arrows. (right) Small bowel series shows the entrapped jejunum between the arrows.



vomiting. Physical examination as well as laboratory studies were essentially within normal limits. Complete barium contrast gastrointestinal evaluation and sigmoidoscopy to 25 cm was negative.

While hospitalized the patient had persistence of abdominal pain and developed periumbilical spasm but with no rebound tenderness. Accordingly an arteriogram was performed (Fig. 1a). The initial interpreta-

tion of the angiogram was possible stenosis of the branches of the lower one third of the jejunum. Exploratory laparotomy was then carried out. However, no stenosis of the arterial branches was noted after thorough examination of the small bowel.

Subsequent review of the angiogram following our experience with Case 2 and Case 3 revealed the jejunal branches actually crossing to the right of the superior mesenteric axis, similar to the finding of the other cases. Review of the small bowel series (Fig. 1b) demonstrated a loop of mid-lower jejunum persistent in location and correlating with the angiogram. In retrospect, reduction of an internal hernia must have been carried out unintentionally in "running" the small bowel at surgery since the patient has remained completely asymptomatic in 30 months followup.

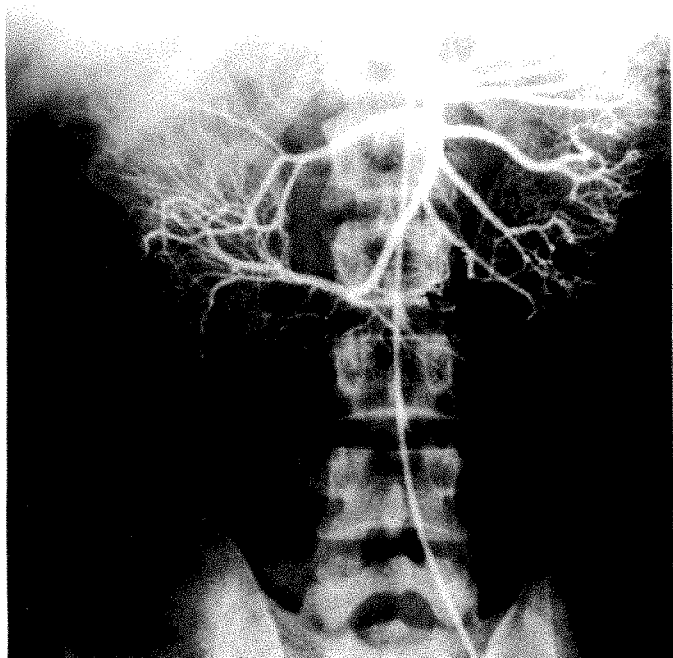


FIG. 2a. Angiography of Case 2 revealing the crossing of the ileal branches to the right of the SMA axis as shown by the arrows.

Case 2: D.J., a 27-year-old Puerto Rican male, had intermittent periumbilical colicky abdominal pain for 18 months prior to his initial admission in April, 1972. Twenty-four months previously he had sustained abdominal trauma in an auto accident. The nature of the pain was not related to any particular foods ingested or time of meals. There was occasional increase in the pain which was relieved by vomiting. His physical examination was unremarkable with no signs of localized peritonitis at the time of initial examination. Barium studies of the gastrointestinal tract were performed and were within normal limits. Abdominal angiography was done during an attack of abdominal pain. This revealed small ileal branches displaying an abrupt change of direction medially and in an upward path to the right of the superior mesenteric axis (Fig. 2a). A small bowel series with barium the following day with the patient still experiencing abdominal pain demonstrated a persistent knuckle of small bowel in the mid-ileum coinciding with the arteriography findings (Fig. 2b).

At the time of surgery a 2.5 cm defect in the root of the small bowel mesentery was noted and repaired with interrupted non-absorbable sutures. The postoperative course was uneventful and the patient has remained asymptomatic for the past 29 months.

Case 3: M.W., a 26-year-old Cuban female, was in good health until



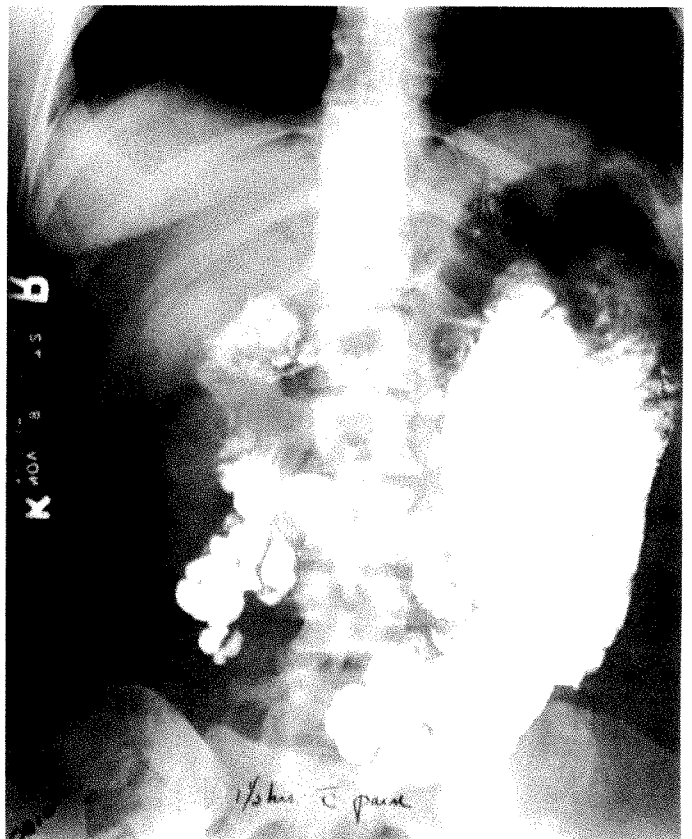
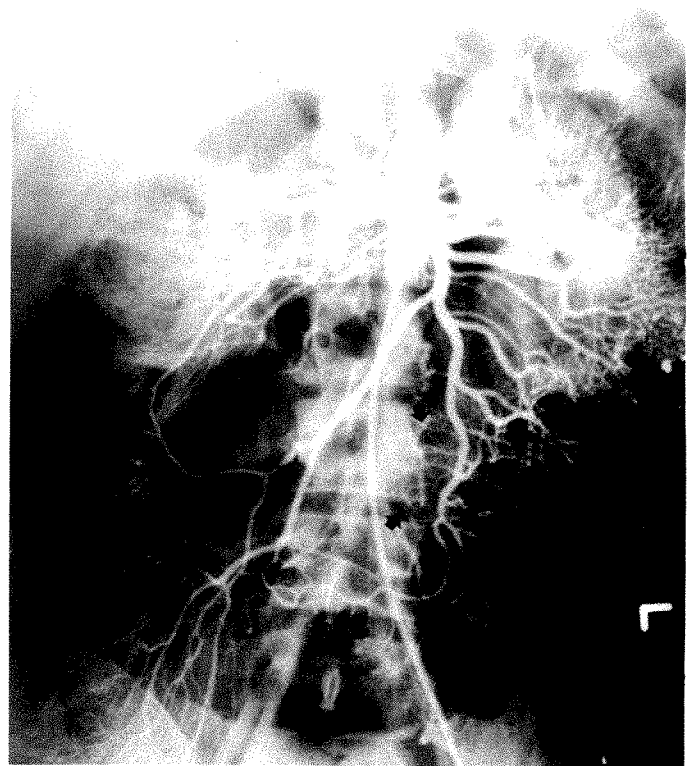
FIG. 2b. Small bowel series shows the entrapped ileal loop between the arrows.

January, 1969, when she began to experience periodic bouts of colicky pain associated with nausea and occasional emesis. Six months previously she had sustained blunt abdominal trauma in a bicycle accident. The abdominal pain was mainly periumbilical and to the left of the midline in location, not precipitated, but aggravated by the ingestion of food. Upper gastrointestinal barium studies demonstrated a probable postbulbar ulcer. At this time she was placed on an intensive medical regimen for peptic ulcer disease and did reasonably well for 3 months. However, in April, 1969, she was readmitted for the onset of severe, colicky abdominal pain. Physical examination revealed only some mid-abdominal tenderness with hyperactive bowel sounds. Laboratory data were within normal limits. Intravenous pyelogram, barium enema, gall bladder series, upper gastrointestinal series with small bowel follow through and sigmoidoscopy to 25 cm were within normal limits. She was discharged on her previous ulcer regimen.

In November, 1972, acute abdominal pain necessitated readmission to the hospital. During this hospitalization abdominal angiography was performed. It revealed a localized group of ileal branches making a hair-pin turn on themselves, crossing the superior mesenteric axis to the right (Fig. 3a). The changes suggested an internal hernia. A small bowel series was done during an episode of abdominal pain which was interpreted as demonstrating no mucosal abnormalities of the small bowel but a suspicious loop in the mid-ileal area that was constant (Fig. 3b). The patient then underwent exploratory celiotomy which revealed a 2.0 cm rent in the root of the small bowel mesentery in the mid-ileal area entrapping small bowel therein. The tear was not through both leaves of the mesentery at that point. The exploration revealed no duodenal ulcer disease. This intramesenteric defect was repaired with non-absorbable sutures. The patient has now done well for 22 months with no recurrence of her periodic intermittent pain and is on no medications.

Discussion

Intra-abdominal herniae are considered protrusions of abdominal viscera into various peritoneal fossa. These may also herniate beyond the limits of the abdominal cavity, such as into the obturator, diaphragmatic or sciatic openings. Developmental anomalies lead to retroperitoneal herniae which occur in the paraduodenal area, omental bursa or pericecal and sigmoidal area. Her-



FIGS. 3a and b. (Top) Angiography of Case 3 revealing the ileal branches crossing to the right of the SMA axis between the two black arrows. (bottom) Small bowel series revealing the ileal loop in the center of the study.

niae may also be acquired from trauma, inflammation or prior surgical intervention.

The exact incidence of internal herniae is unknown. Watson¹² demonstrated 3 in 1,000 autopsies. Exner⁵ reported only 5 of the paraduodenal rotational type in 25,500 autopsies. However, it is quite possible that many go undetected clinically for symptoms may be vague and uncharacteristic of any particular abdominal pain syndrome, and at times these patients may be diagnosed as having psychogenic disorders of the digestive system.

Embryologically at the fifth week of intra-uterine life 3 different parts of the bowel can be identified; the foregut, midgut and hindgut. All three will rotate in later intra-uterine life using as their axis the celiac, superior mesenteric, and inferior mesenteric arteries. Up to the tenth week of intra-uterine life, the midgut migrates into the umbilical pouch rotating 90° counterclockwise; by the tenth week it will return into the peritoneal cavity again, completing its rotation 180° in the same direction. Trietz¹¹ discussed failure of fusion of the peritoneum as a cause for developmental herniae. Moynihan⁹ emphasized the differential pressures between compartments of the peritoneum as the etiology, and Andrews² theorized that all internal hernia were anomalies of intestinal rotation. The later is the most prevalent theory of the etiology of intra-abdominal herniae.

In the case of acute intra-abdominal hernia presenting with signs of complete or incomplete intestinal obstruction clinical manifestations are quite obvious and the treatment is simple. Minimal laboratory and radiographic studies are required and immediate surgery is the treatment of choice.

However, in the chronic cases, symptoms can be so obscure and vague that an intra-abdominal hernia is rarely diagnosed preoperatively. The upper gastrointestinal symptoms usually consist of upper abdominal cramps, nausea and vomiting, which usually occur some time after eating. Clinically, the absence of laboratory signs indicative of inflammatory disease is the rule. Williams¹³ radiographically described displacement or disturbance of small bowel arrangement, sacculaton or clumping, segmental dilatation, stasis, reversed peristalsis and fixation as the hallmarks of internal hernia. Selective abdominal angiography has not been included. All 3 of our cases were discovered by preoperative selective abdominal arteriograms. A case of paraduodenal hernia diagnosed in this fashion will be the subject of a future report.

The 3 case histories presented had several common underlying points. All 3 had similar Hispanic ethnic backgrounds. There are no reports of increased incidence or prevalence of intra-abdominal herniae among Hispanic individuals. Two of them had experienced abdominal trauma prior to the appearance of their chronic pain

syndrome. Physical examinations and laboratory studies were unrevealing and no inflammatory processes were detected. Lastly, all had undergone intensive barium studies in an unsuccessful attempt to clarify the basis for their chronic, periodic abdominal pain, which was periumbilical in location.

Selective abdominal arteriograms were performed in all 3 patients, specifically when the pain was present. In each case small bowel arterial branches were shown to cross to the right of the superior mesenteric axis. In two patients these were ileal branches. This finding is always considered abnormal and is explained by entrapment of small bowel in a peritoneal fossa or mesenteric rent. The angiographic findings were correlated with abnormal small bowel barium series, especially when the pain complex was present. However, it is conceivable that a patient with positive arteriograms could have negative barium studies, particularly when conventional small bowel series are used as demonstrated by Archer *et al.*³ Also, as Alexander¹ has shown, many intra-abdominal herniae are missed because the progress of the barium meal through the small intestine is not observed as carefully and as long as may be necessary.

In two of the cases, exploratory laparotomy eventually supported the presence of mesenteric rents large enough to entrap small bowel. Spontaneous reduction apparently allowed the periodic presentations of abdominal pain with normal radiographic studies. The vagueness of the clinical manifestations coupled with the usual negative ancillary studies are the hallmarks of this problem surgical group. The first patient had exploratory surgery which was considered within normal limits. However, since the defect had been demonstrated on angiography retrospectively, it is felt that during surgery, the hernia was reduced during the normal procedure of running the small bowel without careful examination of the small bowel mesentery at the time of surgery. It should be noted that an intra-abdominal hernia may be spontaneously reduced so that even with correct radiological diagnosis, findings at surgery might be minimal.

The origin of these mesenteric rents may be from three causes. First, an embryological developmental anomaly may exist, creating an abnormally large foramen. Secondly, there may be an abnormally long mesentery allowing undue motility of the intestine and possible traumatic tear, and, thirdly, there may be a combination of the previous. The latter theory would encompass the most likely explanation of the three reported cases herein. The possibility of ethnic specificity for this type of variant of intra-abdominal hernia is also suggested. It is also further suggested from these detailed case reports that this type of intra-abdominal hernia may be more prevalent than previously appreciated. The value of selective abdominal angiography in the evaluation of patients with chronic,

periodic abdominal pain is stressed.

All 3 cases have remained symptom-free in followup for as long as 30 months. Surgical repair should be performed although the end results of repairing these intra-abdominal hernia will be dependent on long term followup. These, possibly traumatic, intra-abdominal hernia may constitute a significant percentage of patients presenting with periodic, chronic abdominal pain previously labeled psychogenic in nature.

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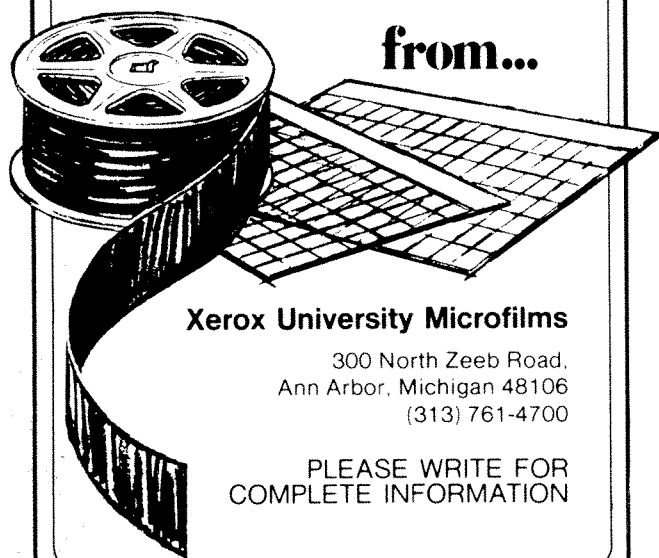
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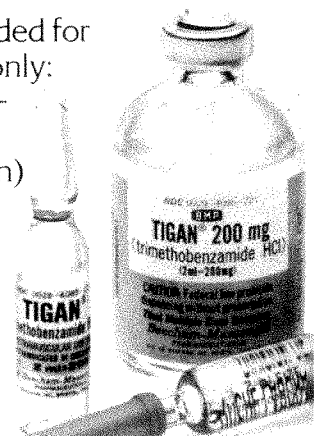
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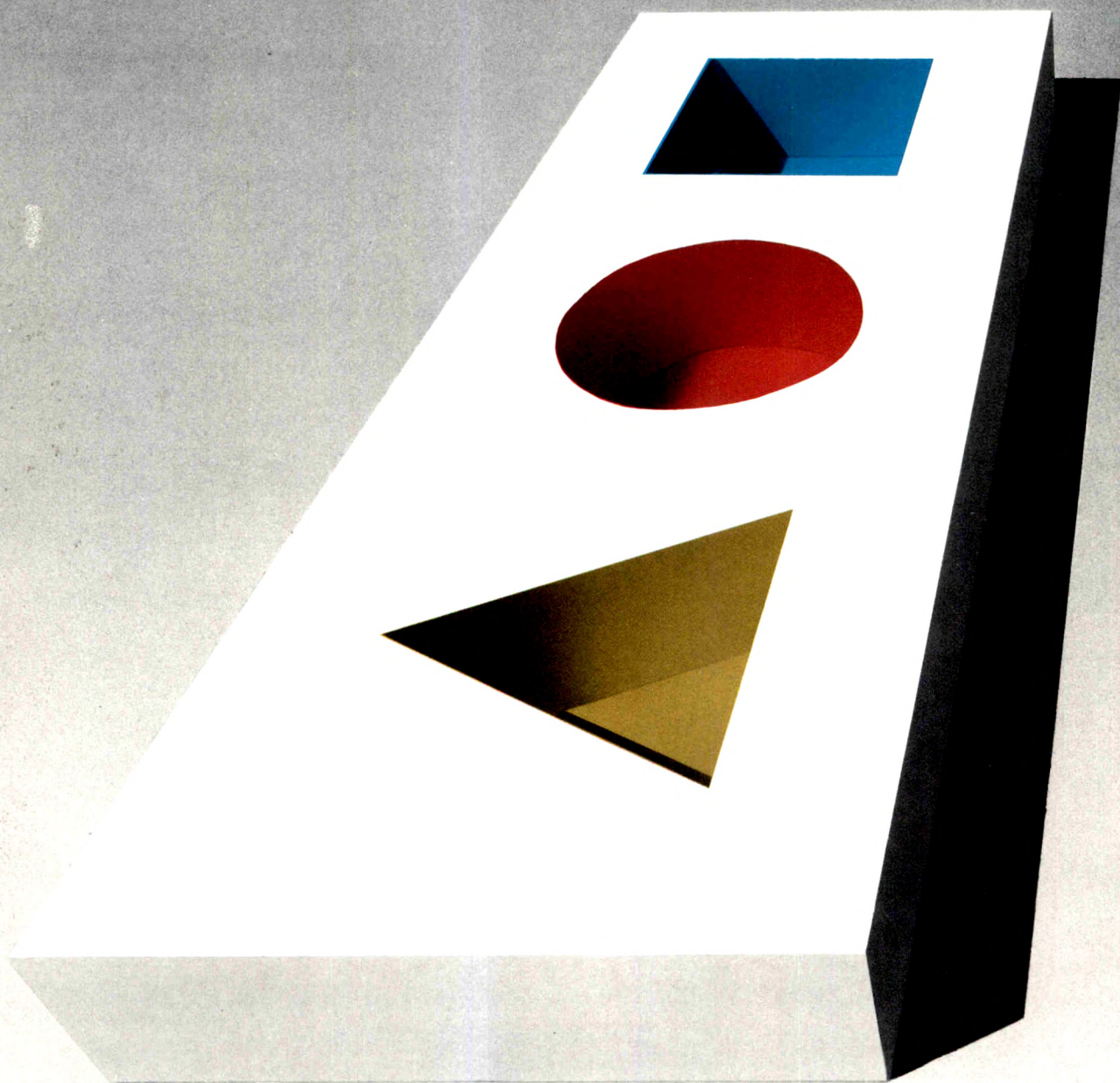
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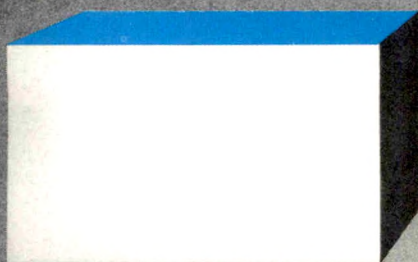
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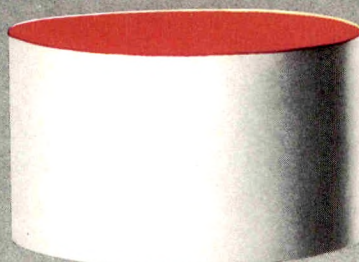


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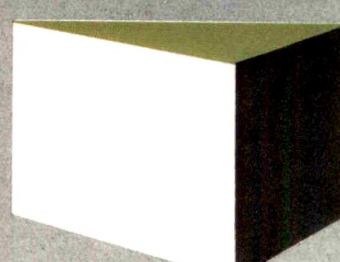


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Haemophilus ducreyi (chancroid), *Pasteurella pestis* and *Pasteurella tularensis*, *Bartonella bacilliformis*, *Bacteroides* species, *Vibrio comma* and *Vibrio fetus*, *Brucella* species (in conjunction with streptomycin). Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

MINOCIN minocycline HCl is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

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MINOCIN is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

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For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the drug of choice, including prophylaxis of rheumatic fever.

Diplococcus pneumoniae.

Staphylococcus aureus, skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infection.

When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to:

Neisseria gonorrhoeae, and *Neisseria meningitidis* (I.V. only), *Treponema pallidum* and *Treponema pertenue* (syphilis and yaws), *Listeria monocytogenes*, *Clostridium* species, *Bacillus anthracis*, *Fusobacterium fusiforme* (Vincent's infection), *Actinomyces* species.

In acute intestinal amebiasis, the tetracyclines may be a useful adjunct to amebicides.

MINOCIN is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may be treated with oral tetracyclines or with a combination of oral and topical agents.

Oral only: In severe acne, the tetracyclines may be useful adjunctive therapy. Minocycline is indicated in the treatment of asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx.

In order to preserve the usefulness of MINOCIN minocycline HCl in the treatment of asymptomatic meningococcal carriers, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and

the correct treatment. It is recommended that the drug be reserved for situations in which the risk of meningococcal meningitis is high.

Minocycline by oral administration is not indicated for the treatment of meningococcal infection.

CONTRAINDICATIONS: This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS: In the presence of renal dysfunction, particularly in pregnancy, intravenous tetracycline therapy in daily doses exceeding 2 grams has been associated with deaths through liver failure.

When the need for intensive treatment outweighs its potential dangers (mostly during pregnancy or in individuals with known or suspected renal or liver impairment), it is advisable to perform renal and liver function tests before and during therapy. Also tetracycline serum concentrations should be followed.

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable. This hazard is of particular importance in the parenteral administration of tetracyclines to pregnant or postpartum patients with pyelonephritis. When used under these circumstances, the blood level should not exceed 15 micrograms/ml. and liver function tests should be made at frequent intervals. Other potentially hepatotoxic drugs should not be prescribed concomitantly.

The use of tetracyclines during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracyclines, therefore, should not be used in this age group unless other drugs are not likely to be effective or are contraindicated.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. Studies to date indicate that photosensitivity does not occur with MINOCIN minocycline HCl.

The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis.

CNS side effects including lightheadedness, dizziness or vertigo have been reported. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and always disappear rapidly when the drug is discontinued.

Usage in Pregnancy. (See above "Warnings" about use during tooth development.)

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in newborns, infants, and children. (See above "Warnings" about use during tooth development.)

All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg./kg. every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

PRECAUTIONS: As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

All infections due to Group A beta-hemolytic streptococci should be treated for at least 10 days.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

ADVERSE REACTIONS: Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region.

These reactions have been caused by both the oral

and parenteral administration of tetracyclines. **Skin:** Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. **Renal sensitivity** is discussed above. (See "Warnings.") **Renal toxicity:** Rise in BUN has been reported and is apparently dose related. (See "Warnings.") **Hypersensitivity reactions:** Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus. Bulging fontanels have been reported in young infants following full therapeutic dosage. This sign disappeared rapidly when the drug was discontinued. **Blood:** Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. **CNS:** (See "Warnings.") When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSEAGE AND ADMINISTRATION: ORAL. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided.

Concomitant therapy: Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given to patients taking oral tetracycline.

Studies to date have indicated that the absorption of MINOCIN is not notably influenced by foods and dairy products.

In patients with renal impairment: (See "Warnings.") Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

In the treatment of streptococcal infections, a therapeutic dose of tetracycline should be administered for at least 10 days.

Adults: The usual dosage of MINOCIN minocycline HCl is 200 mg. initially followed by 100 mg. every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg. capsules may be given initially followed by one 50 mg. capsule four times daily.

Children: The usual dosage of MINOCIN minocycline HCl is 4 mg./kg. initially followed by 2 mg./kg. every 12 hours.

For treatment of syphilis, the usual dosage of MINOCIN should be administered over a period of 10-15 days. Close follow-up, including laboratory tests, is recommended.

Gonorrhea patients sensitive to penicillin may be treated with MINOCIN, administered as 200 mg. initially followed by 100 mg. every twelve hours for a minimum of 4 days, with post-therapy cultures within 2-3 days.

In the treatment of meningococcal carrier state recommended dose is 100 mg. every 12 hours for five days.

DOSEAGE AND ADMINISTRATION: INTRAVENOUS. **Note:** Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not adequate or tolerated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

Adults: Usual adult dose: 200 mg. followed by 100 mg. every 12 hours and should not exceed 400 mg. in 24 hours. The drug should be initially dissolved and then further diluted to 500-1,000 cc. with either Sodium Chloride Injection USP, Dextrose Injection USP, Dextrose and Sodium Chloride Injection USP, Ringer's Injection USP, or Lactated Ringer's Injection USP but not in other solutions containing calcium (a precipitate may form).

The reconstituted solutions are stable at room temperature for 24 hours without significant loss of potency. Any unused portions must be discarded after that period. The final dilution for administration should be administered immediately.

Children: Usual pediatric dose: 4 mg./kg. followed by 2 mg./kg. every 12 hours.

In patients with renal impairment: (See "Warnings.") Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

HOW SUPPLIED: CAPSULES—Minocycline Hydrochloride equivalent to 100 mg. Minocycline. Hardshell purple and orange. Bottles of 50, 100 and Unit Dose 10 x 10's. Product No. 5301.

Minocycline Hydrochloride equivalent to 50 mg. Minocycline. Hardshell orange. Bottles of 100 and Unit Dose 10 x 10's. Product No. 5300.

SYRUP—Minocycline Hydrochloride equivalent to 50 mg. Minocycline per teaspoonful (5 cc.). Preserved with propylparaben 0.10% and butylparaben 0.06% with Alcohol USP 5% v/v. Custard-flavored in bottles of 2 fl. oz. Product No. 5313.

INTRAVENOUS—100 mg. vials of sterile cryodesiccated powder. Product No. 5305. (Combined 10/74)

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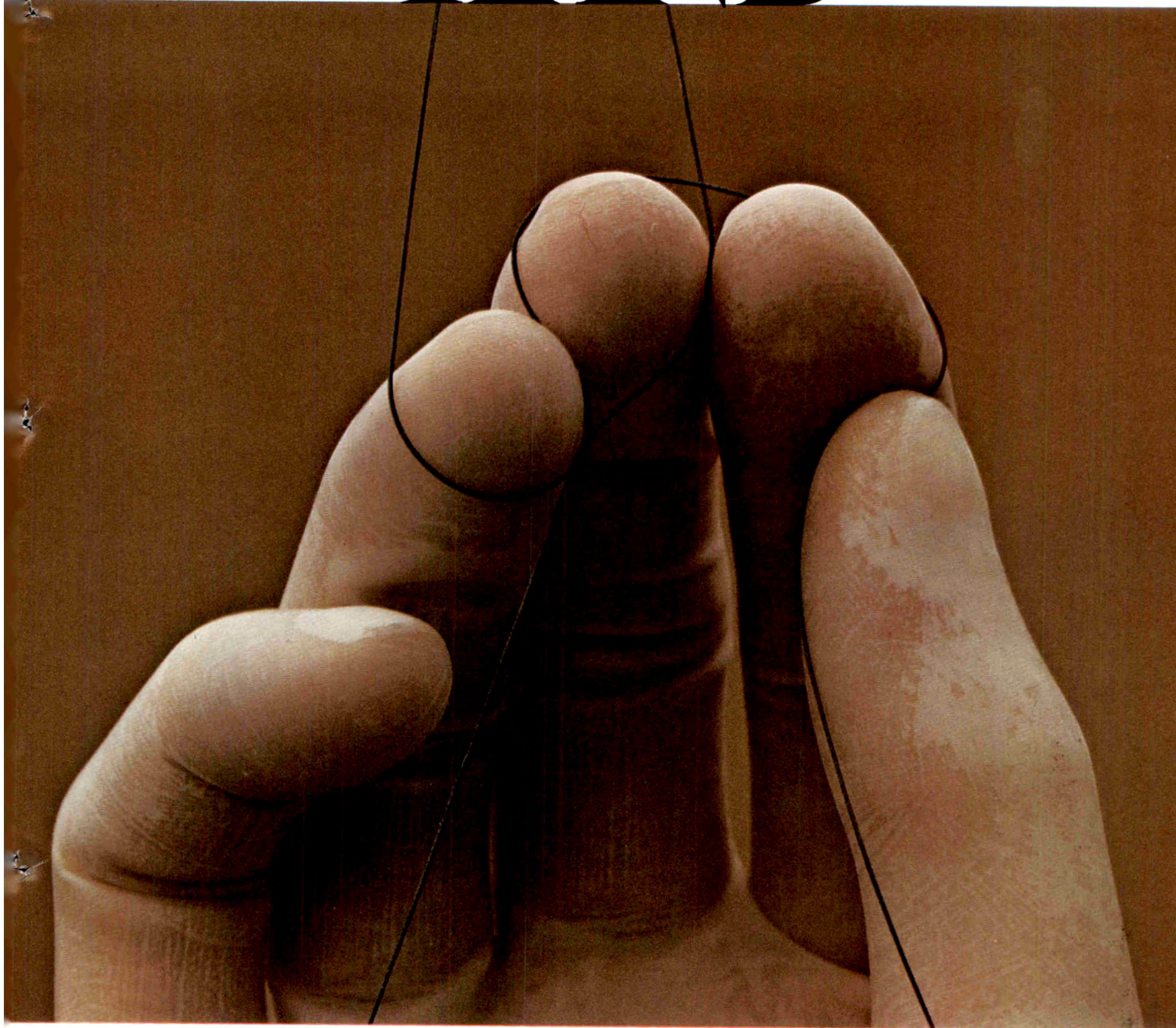
MILITARY NSN 6505-00-003-5112 (50's)

VA NSN 6505-00-003-5112A 100 mg. capsules

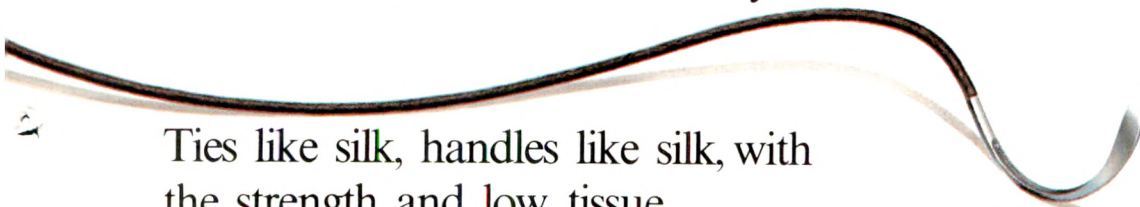
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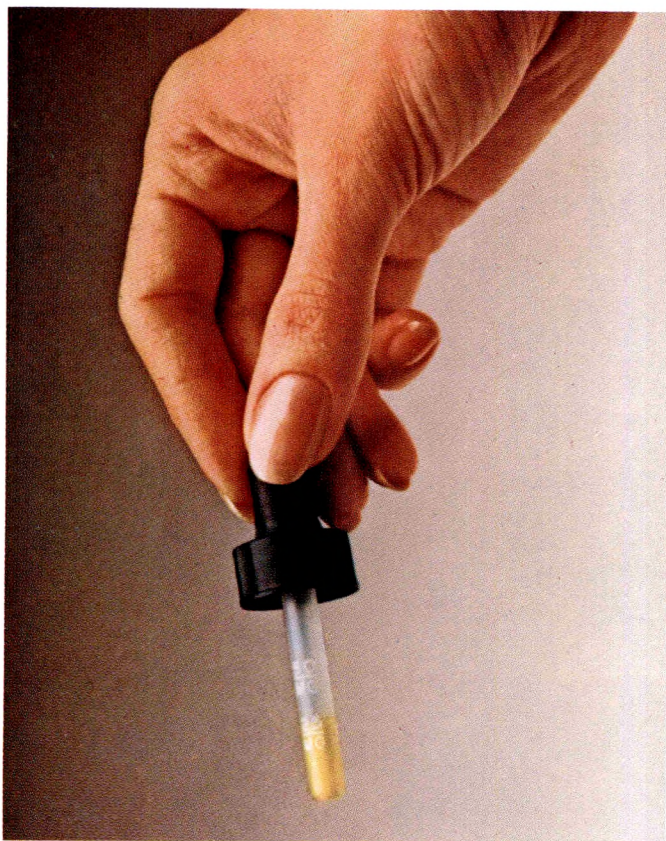
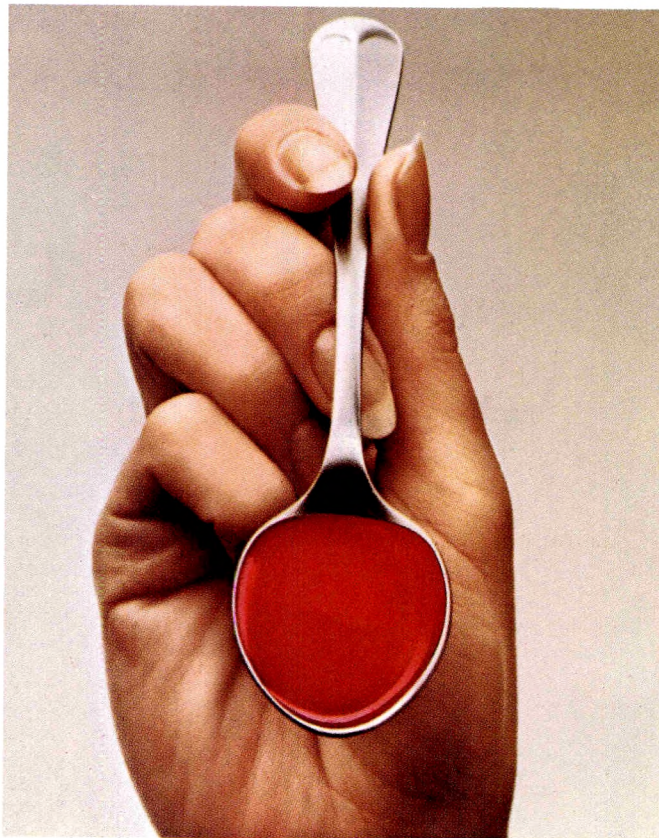
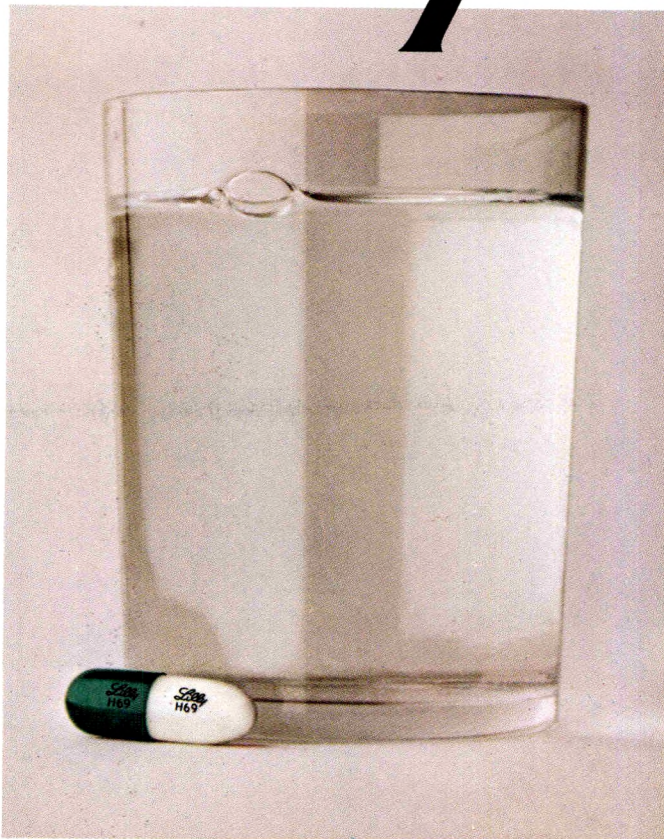
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Development and Treatment of Post-traumatic Pulmonary Platelet Trapping

RICHARD M. PEER, M.D., SEYMOUR I. SCHWARTZ, M.D.

In anesthetized dogs soft tissue trauma resulting in hypovolemia was associated with pulmonary trapping of ^{51}Cr tagged platelets. The efficacy of various forms of therapy aimed at preventing pulmonary trapping of platelets following trauma was evaluated. Lung biopsies were assayed before trauma and at hourly intervals for accumulation of autologous ^{51}Cr tagged platelets reinfused 24 hours prior to the experiment. The study showed that pulmonary platelet trapping secondary to soft tissue trauma could be prevented by treatment with Dextran 40, Dextran 70 and methylprednisolone administered one hour after trauma and by pretreatment with aspirin.

RESPIRATORY INSUFFICIENCY is recognized as a major complication which may follow serious illness or trauma. The Respiratory Distress Syndrome (R.D.S.), as described by Blaisdell,⁵ develops within the first 24 to 48 hours after injury. Tachypnea is associated with progressive fall in arterial PO_2 . There are characteristic radiographic findings and microscopic demonstration of platelet aggregates within capillaries and fibrin in alveoli.⁶ The precise etiology of the syndrome has yet to be defined. Oxygen toxicity, shock, fluid overload, direct pulmonary trauma, emboli, and other factors have been implicated.

Many reports have emphasized microemboli as one of the etiologic factors in the R.D.S.^{6,17} Experimentally, microemboli have been shown to appear in the circulation following acute trauma.¹⁹ Arfors³ used laser-induced endothelial trauma to demonstrate the formation of platelet aggregates at the site of injury as well as their embolization. Allardyce² employed microradiography to demonstrate decrease in pulmonary capillary and arterio-

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lar filling due to microemboli following hemorrhagic shock in rabbits. Ljungqvist¹⁴ found increased platelet adhesiveness and aggregability after both hemorrhagic shock and hypotension induced by soft tissue trauma. Ljungqvist¹⁵ also demonstrated an accumulation of labeled platelets in serial lung biopsies following soft tissue trauma in dogs.

The current studies were designed to evaluate pulmonary trapping of platelets and fibrinolysin activity after injury and traumatic shock in dogs. Experiments were also conducted to test the efficacy of various forms of therapy in preventing post-traumatic pulmonary platelet trapping. Agents used included heparin, methylprednisolone, aspirin (ASA), both as pretreatment and after trauma, Dextran 40 (D 40) and 70 (D 70), and Ringer's Lactate (RL) solution.

Materials and Methods

The experiments were conducted on mongrel dogs weighing 18-22 Kg. On the day prior to experiment, 300 ml of whole blood was withdrawn and centrifuged to isolate the platelets, which were then tagged *in vitro* with ^{51}Cr according to the method modified by Abrahamsen.¹ The labeled platelets as well as red cells were then reinfused.

The dogs previously tagged with ^{51}Cr platelets were anesthetized with I.V. Pentobarbital and ventilated through an endotracheal tube. Cannulas were inserted into a carotid artery and jugular vein. A right thoracotomy was performed for obtaining lung biopsies. The pulmonary artery was cannulated through the pul-

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TABLE 1. Hemodynamic and Hematologic Changes Associated with Trauma Model

	SA (mm/Hg)	PA (mm/Hg)	Hct - %	PC	Blood ^{51}Cr %	Lung ^{51}Cr %
Before Trauma	148 $\pm$ 9	15 $\pm$ 2	39 $\pm$ 1	100,000	100	38 $\pm$ 4
After Trauma, 1 hr	84 $\pm$ 10	21 $\pm$ 3	42 $\pm$ 1	88,000	98 $\pm$ 6	54 $\pm$ 8
After trauma, 2 hr	100 $\pm$ 9	21 $\pm$ 3	44 $\pm$ 2	90,000	109 $\pm$ 3	66 $\pm$ 6
After trauma, 3 hr	110 $\pm$ 8	25 $\pm$ 3	45 $\pm$ 2	100,000	100 $\pm$ 6	65 $\pm$ 6
After trauma, 4 hr	111 $\pm$ 3	21 $\pm$ 1	46 $\pm$ 1	107,000	106 $\pm$ 4	71 $\pm$ 8

Traumatized control group (H = 4).

^{51}Cr values expressed as percent of normalized pre-trauma blood value.

monary outflow tract. The systemic artery (S.A.) and pulmonary artery pressures (P.A.) were monitored continuously on a Sanborn multi-channel recorder. Dogs which were anesthetized and maintained under anesthesia throughout the entire procedure underwent soft tissue trauma using a technique described by Cannon and Bayliss.⁹ Two hundred blows were administered to each hind limb with a two pound, padded wooden mallet. Before trauma, duplicate 1 ml arterial and venous blood samples and 0.2 to 0.4 gram lung biopsies were obtained for determination of ^{51}Cr activity. Additional samples were collected at hourly intervals for 4 hours after trauma. Hematocrit (Hct) and platelet counts (P.C.) were recorded at the time of sampling. Samples of blood for fibrinogen split products were drawn before trauma and 4 hours after injury and the split products were measured according to the method of Merskey.¹⁶ The ^{51}Cr activity was measured in a Gamma well scintillation counter and calculated as radioactivity per gram of tissue. All the results were standardized by setting the activity of the initial arterial blood sample to 100%.

Four untraumatized dogs served as a control for ^{51}Cr distribution. Two of them were untreated and two were hydrated with Dextran 40 (D-40), 20 ml/kg for one hour. Each traumatized group contained 4 dogs. One group underwent no further manipulation and was observed for 4 hours. Groups were resuscitated with R.L. (40ml/kg) D-40 (20 ml/kg), and D-70 (20 ml/kg). Others received heparin, (2mg/kg) ASA (325 mg/rectally) and methylprednisolone (30mg/kg). All therapy was initiated one hour after trauma. One group was pretreated with ASA, 325 mg P.O. after reinfusion of the tagged platelets 24 hours before trauma. Statistical analysis was carried out using the student *t* test where applicable.

TABLE 2. Fibrinogen Split Products

Group	Before Trauma	4 Hrs After Trauma	"P"
Control	14.7 $\pm$ 4.9	23.3 $\pm$ 3.3	<0.1
R.L.	12.0 $\pm$ 2.4	20.0 $\pm$ 5.5	<0.1
D-40	20.0 $\pm$ 7.1	35.0 $\pm$ 5.0	<0.1
D-70	8.75 $\pm$ 1.25	32.5 $\pm$ 16.0	<0.1
Pre-ASA	10.0 $\pm$ 0.0	15.0 $\pm$ 2.89	<0.1
ASA	15.0 $\pm$ 2.9	25.0 $\pm$ 5.0	<0.1
Solumedrol	15.0 $\pm$ 2.9	27.5 $\pm$ 7.5	<0.1

Results

In the untraumatized control dogs, the Hct increased from 37% to 41% over 4 hours. The S.A. pressure and P.A. pressures remained unchanged. The blood level of ^{51}Cr remained at 100 $\pm$ 4% and the lung ^{51}Cr value was stable at 37 $\pm$ 4%. In the untraumatized D-40 hydrated dogs, the Hct fell from 41 to 32% over 4 hours. The SA and PA remained stable. The blood ^{51}Cr activity decreased to 76% while the lung value remained at 33 $\pm$ 4%.

In the traumatized control group (Table 1), the injury resulted in a fall in SA pressure from 148 $\pm$ 9 to 111 $\pm$ 3mm Hg ($P < 0.001$) 4 hours after trauma. The PA pressure increased from 15 $\pm$ 1 to 21 $\pm$ 1. The hematocrit rose from 39 $\pm$ 1 to 46 $\pm$ 1%. The platelet count fell from 100,000 to 88,000/ml at one hour after trauma and rose to 107,000 at 4 hours. The radioactivity of the arterial and venous samples was similar in all experiments. In the trauma control series, the ^{51}Cr value in circulating blood increased insignificantly from 100 to 106%. However, there was a significant accumulation of ^{51}Cr tagged platelets in the lungs: 38 $\pm$ 4 to 71 $\pm$ 8% ($P < 0.001$) (See Fig. 1).

In all experiments the changes in pressures, Hct, and P.C. were similar. In all dogs, the injury resulted in a

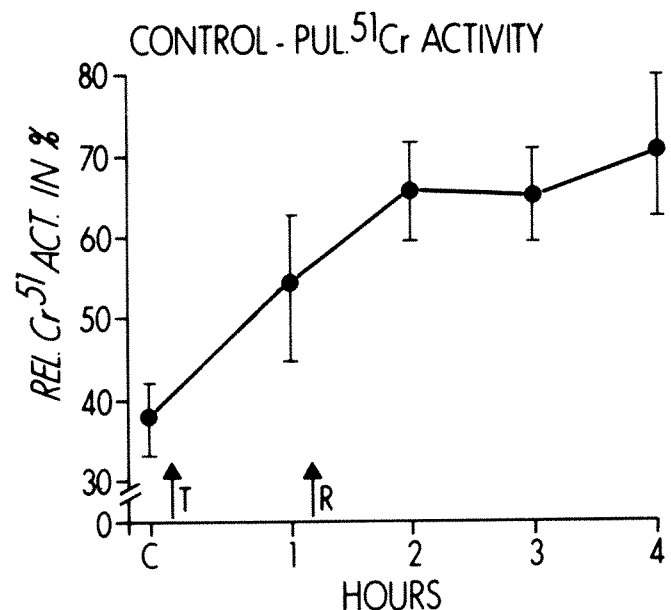
FIG. 1. Changes in ^{51}Cr activity (labelled platelets) during 4 hour exper-

TABLE 3. Relative ^{51}Cr Activity in Arterial Blood Normalized to 100%

	Before Trauma	After Trauma			
		1 hr	2 hr	3 hr	4 hr
Control	100	98 $\pm$ 6	109 $\pm$ 3	100 $\pm$ 6	106 $\pm$ 4
L.R.	100	99 $\pm$ 5	85 $\pm$ 2	87 $\pm$ 7	89 $\pm$ 6
D-40	100	103 $\pm$ 10	74 $\pm$ 5	79 $\pm$ 4	87 $\pm$ 4
D-70	100	101 $\pm$ 4	77 $\pm$ 2	76 $\pm$ 2	76 $\pm$ 4
Heparin	100	99 $\pm$ 6	111 $\pm$ 5	113 $\pm$ 2	126 $\pm$ 6
Pre Rx ASA	100	100 $\pm$ 6	113 $\pm$ 6	109 $\pm$ 7	123 $\pm$ 5
ASA	100	107 $\pm$ 6	112 $\pm$ 6	115 $\pm$ 5	111 $\pm$ 6
Methylprednisolone	100	96 $\pm$ 5	109 $\pm$ 4	113 $\pm$ 5	112 $\pm$ 4

mean fall in S.A. pressure from 141 ± 4 to 85 ± 2 mm Hg ($P < 0.001$) one hour after trauma. Dogs rehydrated with R.L., D-40, and D-70 showed a return in S.A. pressure to 138 ± 3 and a slight elevation in P.A. pressure from 15 ± 3 to 23 ± 2 mm Hg. In the remainder of the dogs, the P.A. increased to 20 ± 1 . The mean hematocrit was $40 \pm 1\%$ before trauma and rose to 46 ± 1 over the 4 hours after trauma. In the resuscitated animals, the Hct fell to 34 ± 1 .

The platelet counts fell from a mean of $210 \times 10^3/\text{ml}$ to $190 \times 10^3/\text{ml}$ ($P < 0.05$) one hour after trauma in all dogs. In the volume treated groups it continued to fall; however, the level in the remaining dogs returned to pre-trauma values. After trauma, there was a consistent increase ($P < 0.1$) in the split products in the blood in all groups, control and treated (Table 2).

In the heparin, aspirin, methylprednisolone and the ASA pre-treatment groups the blood activity increased by 16%. In the fluid resuscitated groups of blood activity decreased 20% (Table 3).

Data on the lung ^{51}Cr activity are presented in Table 4. In the groups treated with heparin, ASA (rectally), and R.L., the extent of platelet accumulation in lung was similar to that determined for untreated animals. In the Heparin group, the ^{51}Cr activity increased from 60 ± 2 to 67 ± 9 ($P < 0.001$). In the group given ASA, the ^{51}Cr activity increased from 33 ± 3 to 53 ± 4 ($P < 0.001$). Similar findings were noted in the group resuscitated with R.L.: the ^{51}Cr activity increased from 42 ± 3 to 60 ± 10 ($P < 0.01$) (Figs. 2 and 3).

In the dogs resuscitated with D-40 there was no significant increase in lung ^{51}Cr activity: 40 ± 8 to 30 ± 8 . Similar findings were noted with D-70: 32 ± 6 to 30 ± 5 (Fig. 4). Treatment with methylprednisolone one hour after trauma prevented pulmonary platelet trapping: 29 ± 4 to 35 ± 11 (Fig. 5). Pre-treatment with aspirin was successful in preventing post-traumatic pulmonary platelet accumulation: 37 ± 7 to 41 ± 5 (Fig. 2).

Discussion

In this experimental model, as originally described by Cannon and Bayliss,⁹ the initially proposed mechanism for shock was related to humoral factors released from the injured tissue. However, Blalock⁷ later proved that the soft tissue injury resulted in hypovolemic shock due

to loss of plasma and formation of edema at the site of injury. In the current studies the method resulted in marked edema of the thighs with some minor hemorrhages. In no instance was there rupture of a major vessel or femoral fracture. The subsequent consistent fall in systolic blood pressure and concurrent rise in hematocrit were reversed by volume replacement using R-L, D-40 and D-70, thus substantiating the hypovolemic concept.

Blood platelets are produced by the megakaryocytes found primarily in bone marrow and occasionally in the pulmonary microcirculation. One third of the available platelets are in the circulating blood and the remainder in "pools", i.e., primarily spleen, and to some extent lung. The platelets normally play an integral role in initiating coagulation. Following endothelial injury, the platelets become adhesive and stick to exposed collagen, elastin and basement membrane. The activated platelets then undergo a release reaction. Among other substances released, ADP, a potent platelet aggregator, stimulates

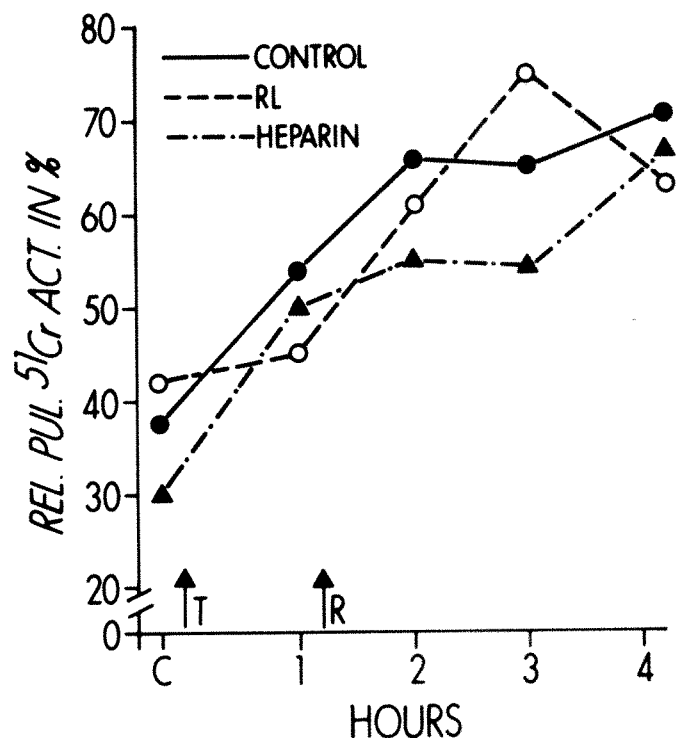


FIG. 2. Changes in ^{51}Cr activity (labelled platelets) during 4 hour experiment: RL and Heparin treatment.

TABLE 4. Relative Pulmonary ^{51}Cr Activity in %

	Control	R.L.	D-40	D-70	Heparin	Pre-Rx ASA	ASA	Methylprednisolone
Before trauma	38 $\pm$ 4	42 $\pm$ 3	40 $\pm$ 8	32 $\pm$ 6	30 $\pm$ 2	37 $\pm$ 7	33 $\pm$ 3	29 $\pm$ 4
Control								
After trauma 1 hr	54 $\pm$ 8	45 $\pm$ 5	43 $\pm$ 6	43 $\pm$ 5	50 $\pm$ 1	41 $\pm$ 5	40 $\pm$ 4	25 $\pm$ 1
After trauma 2 hr	66 $\pm$ 6	61 $\pm$ 6	29 $\pm$ 5	37 $\pm$ 5	55 $\pm$ 12	45 $\pm$ 4	53 $\pm$ 3	35 $\pm$ 6
After trauma 3 hr	65 $\pm$ 6	75 $\pm$ 12	31 $\pm$ 5	36 $\pm$ 2	54 $\pm$ 5	50 $\pm$ 2	69 $\pm$ 10	38 $\pm$ 12
After trauma 4 hr	71 $\pm$ 8	60 $\pm$ 10	30 $\pm$ 8	30 $\pm$ 5	67 $\pm$ 9	41 $\pm$ 5	58 $\pm$ 4	35 $\pm$ 11

further platelet aggregation. The release of platelet factor 3 triggers the plasma coagulation system, thus initiating fibrin deposition. In addition to their direct role in hemostasis, the platelets may become activated by various stimuli, such as epinephrine, collagen, thrombin, and ADP. These stimulate the further release of ADP as well as fibrinogen and nucleotides, all of which promote platelet aggregation.¹³

In this trauma model, injury to the hind limb presumably damages vascular endothelium, thereby exposing and disrupting collagen. Platelet aggregates are formed and embolize to be subsequently screened by the pulmonary vasculature. The changes in platelet counts reflect local consumption as well as splenic release of stored pools in the face of shock.

Aspirin is known to reduce platelet stickiness as measured by the glass bead retention test. Weiss²⁰ has shown that ASA depresses platelet aggregation in response to collagen as well as blockage of the release reaction. Zucker²² has demonstrated a prevention of the second wave of aggregation in response to epinephrine by pretreatment with aspirin. A single dose of aspirin has been shown to affect an entire population of platelets for approximately 4 days, the half-life of the platelets.²⁰ In the present study, pretreatment with aspirin blocked the accumulation of platelets in canine lungs after trauma. On the other hand, rectally administered aspirin following trauma had no effect, presumably due to slow absorption and length of the experiment.

Dextran 40 and 70 decrease platelet retention in a glass

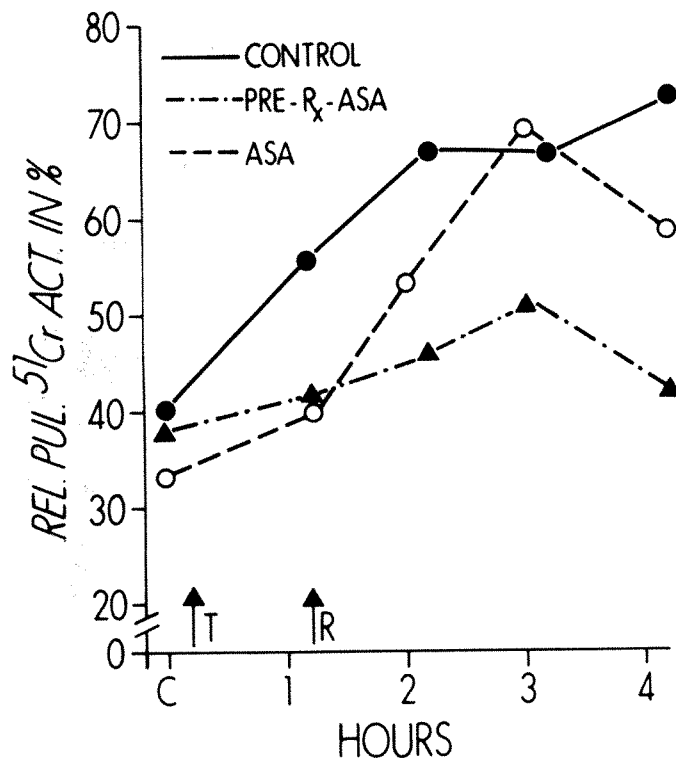


FIG. 3. Changes in ^{51}Cr activity (labelled platelets) during 4 hour experiment: Aspirin treatment and pretreatment.

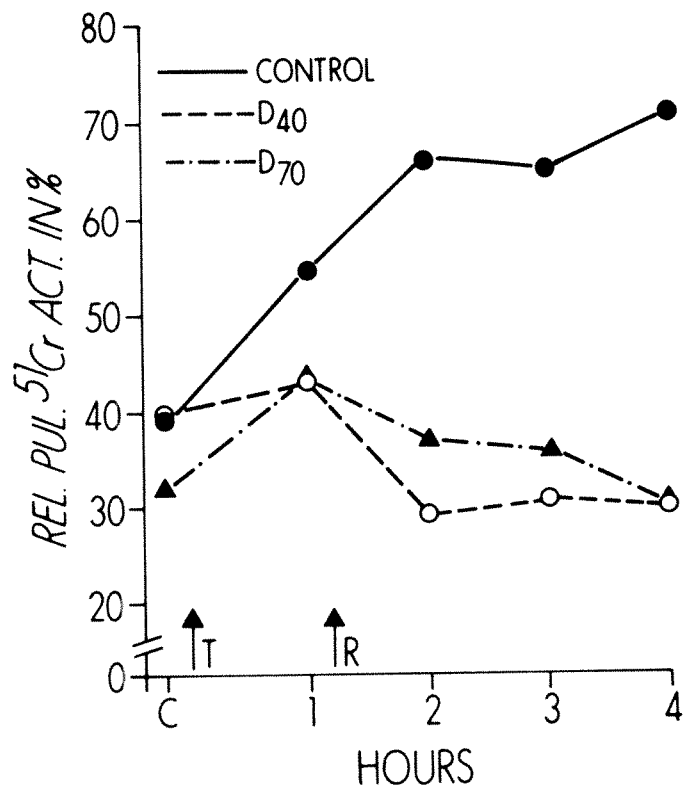


FIG. 4. Changes in ^{51}Cr activity (labelled platelets) during 4 hour experiment: D-40 and D-70 treatment.

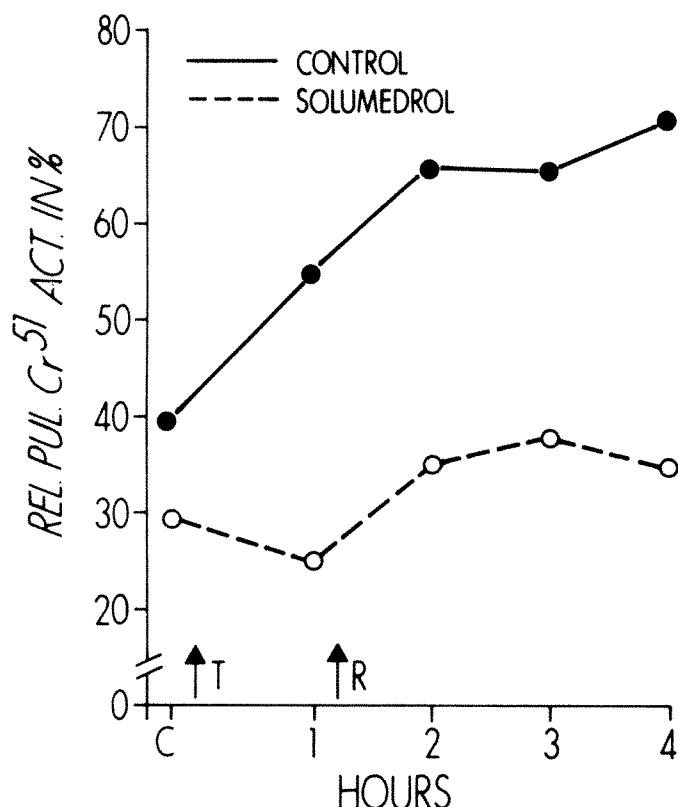


FIG. 5. Changes in ⁵¹Cr activity (labelled platelets) during 4 hour experiment: Solumedrol treatment.

bead column.⁴ Both Dextran 40 and 70 appear to increase the negative surface charge of the platelets and thereby decrease adhesion and aggregation.¹⁹ Dextran 70 has been shown to be more effective than Dextran 40 in altering platelet function,⁸ but with methods of resuscitation using Dextran 40 and 70 in the current study, there was a similar inhibition of posttraumatic pulmonary platelet trapping.

Corticosteroids have been shown to be effective in stabilizing cell membranes and in altering some of the pulmonary changes resulting from shock.²¹ Steroids appear to decrease the platelet release reaction and thereby decrease the formation of platelet aggregates. In this study, the dogs treated with methylprednisolone failed to accumulate ⁵¹Cr platelets in the lungs after trauma.

The exact effect of heparin on platelets is unclear. Heparin alone can initiate aggregation.¹⁰ Low doses of heparin increase adhesiveness while high doses decrease it.¹² In the amounts used for the present study, heparin did not alter the post-traumatic pulmonary platelet trapping.

Hedner¹¹ has reported an increase in fibrinogen split products in association with numerous diseases and proposed using split product determinations as an index of pathological conditions. In the current experiments the split products were elevated after trauma in all dogs irrespective of the form of therapy and the extent of pulmonary platelet trapping. This suggests that fibrino-

lytic activity in response to microemboli resulting from trauma is not related to the extent of platelet sequestration in the lung.

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Boerhaave Syndrome:

Report of a Case Treated Non-operatively

ALBERTO J. LARRIEU, M.D., RICHARD KIEFFER, M.D.

An unique case of Boerhaave's Syndrome is presented in which the patient survived without any surgical treatment. We believe that this was due to non-contamination of the mediastinal and pleural cavities as shown by serial contrast roentgenograms of the esophagus.

SPONTANEOUS RUPTURE of the non-diseased esophagus is associated with a catastrophic and almost always fatal course unless promptly diagnosed and treated with extensive surgical measures.

We wish to report a typical presentation of such a case but treated without thoracotomy or chest drainage and resulting in survival.

Case Report

On August 2, 1974, N.R., a 57-year-old Caucasian male alcoholic was admitted to another hospital with a presumptive diagnosis of bleeding or perforated duodenal ulcer vs. acute pancreatitis. The patient, at that time, gave history of drinking 5-6 beers during the day and starting to vomit blood that same night. However, further questioning a few days later revealed that the patient had to strain and retch "like never before" just prior to vomiting. He also stated later that he "had felt something tear" subternally on his first episode of vomiting stating he experienced these same events three times, each time bringing up "about one pint of blood" before he was admitted to the hospital.

Physical examination on admission was unremarkable except for the fact that he had tenderness over the epigastrium but with normal bowel sounds. Laboratory results at the time showed a normal serum amylase (75 U), slightly elevated 2 hour urinary amylase (535 U), borderline serum lipase, WBC count of 15,000/mm³, hemoglobin of 14 gms and a hematocrit of 42%. Abdominal roentgenograms showed no air in the abdominal cavity and the chest x-ray was initially interpreted as normal.

On the third day post rupture, August 5, the patient was noticed to

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have subcutaneous emphysema of the right supraclavicular area and repeated films of the chest revealed the presence of subcutaneous emphysema and a pneumomediastinum. At this time, review of the admitting chest x-ray showed mediastinal air. A gastrografin swallow performed shortly after this demonstrated a low esophageal perforation with mediastinal air. Chest x-ray revealed a left pleural effusion.

It was immediately felt at that institution that an operation was indicated for mediastinal drainage and possible repair of the perforation and this was explained to the patient. The patient agreed but because of financial difficulties asked to be transferred to Baltimore Veterans Administration Hospital. Meanwhile, he was started on Keflin 1 gm IV and Gentamycin 60 mgms IM.

On admission to Baltimore VA hospital on August 7, just 5 days post rupture, the patient was in good condition, denying pain or malaise and without any history of chills and fever. On physical examination the vital signs were within normal limits, the chest revealed increased dullness to percussion and diminished breath sounds at the left lung base and the abdomen was conspicuous for the absence of findings. The patient was admitted with the diagnosis of spontaneous rupture of the esophagus and placed NPO, treated with intravenous fluids and kept on the same antibiotics. Admitting laboratory data was found to be within normal limits except for a slight elevation of the serum amylase to 418 U (N-70-300 U/L). Also the WBC count was 13,000/mm³ and the liver function tests were within normal limits.

We elected to observe this patient in view of his stable course and in the absence of evidence of spreading infection either in the mediastinum or in the pleural cavities. It was understood that at the first sign of increasing toxicity surgical drainage would be undertaken.

Chest films revealed the already described left pleural effusion (Fig. 1). On follow-up films this effusion remained unchanged until August 12, 10 days post rupture when it was noted to diminish in size with only a small amount of residual fluid remaining in the posterolateral left costophrenic angle (Fig. 2).

On August 15, 13 days post rupture, a barium swallow demonstrated (Fig. 3) extravasation of contrast media from the distal esophagus just above the diaphragm, being confined to a space measur-

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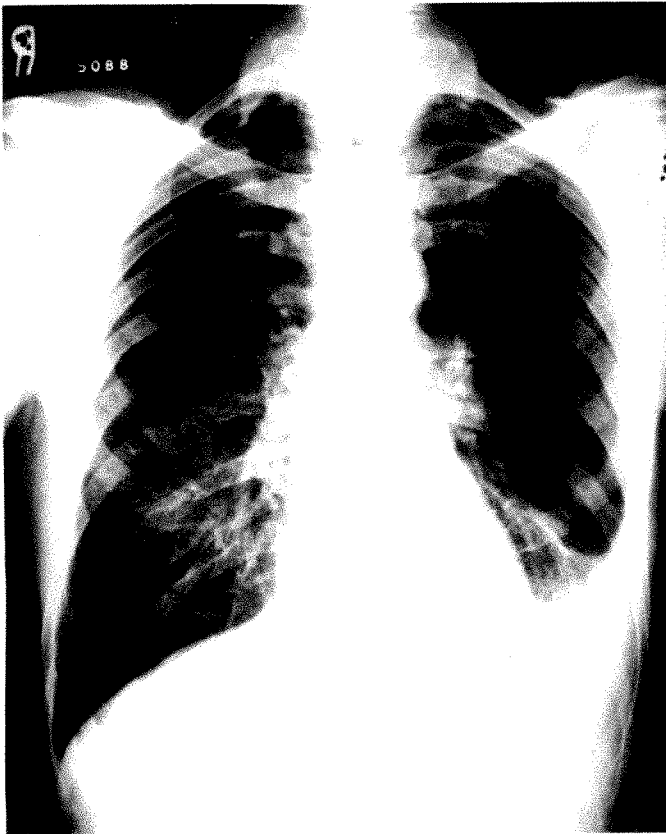


FIG. 1. Chest x-ray on admission to Veterans Administration Hospital revealing left pleural effusion.

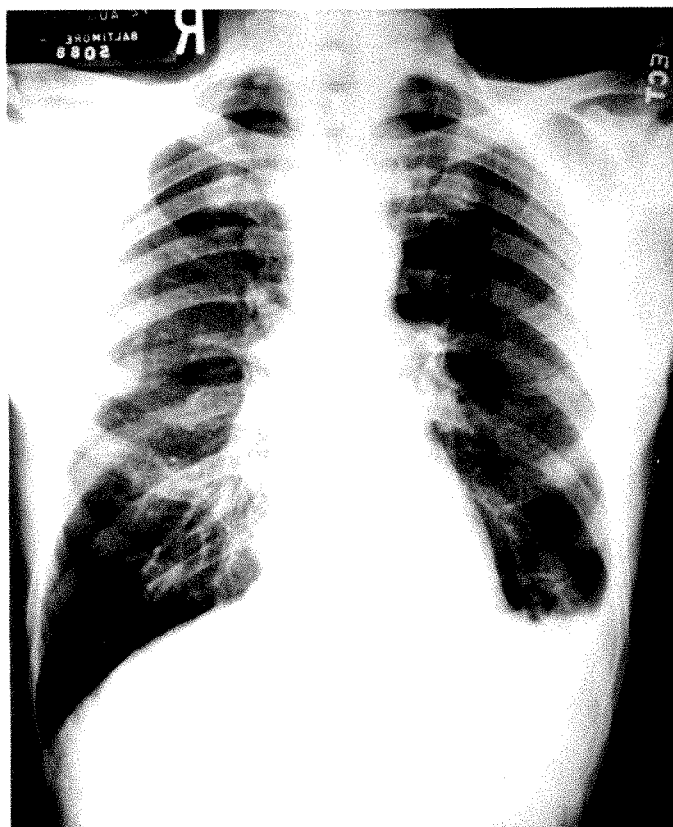


FIG. 2. Chest x-ray 10 days post rupture of esophagus, showing a reduction in the left pleural effusion.

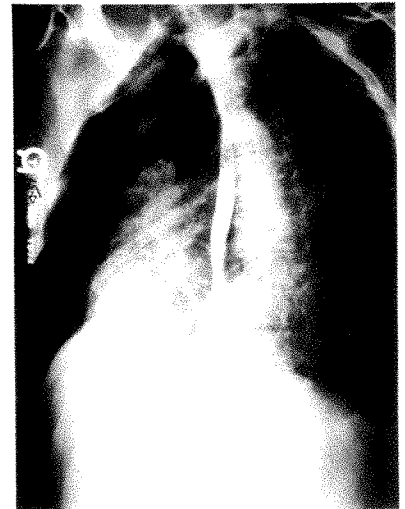


FIG. 3. Barium swallow, 13 days post rupture, demonstrating the confined extravasated contrast media.

ing 6 cm long and 2 cm wide to the left and posterior to the esophagus extending proximally to the left of the vertebral column. It appeared to be confined to this area with no evidence of spread even in the lateral projection. A subsequent heavily exposed film of the lower thorax performed 5 hours later revealed no residual barium in the region of the esophagus, or in the area of extravasation previously noted.

By this time, the left pleural effusion had completely resolved and the patient was afebrile and asymptomatic. The antibiotics had been discontinued the previous day, after a 10 day course, and he was started on a clear liquid diet. Since he tolerated this well and his clinical course remained unchanged, he was advanced to a full liquid diet.

On the 21st of August, another barium swallow showed marked improvement since the previous study with only a small channel filled with barium remaining, measuring 4 cm long and less than $\frac{1}{2}$ cm wide and communicating with the epiphrenic portions of the esophagus (Fig. 4).

The patient was placed on a regular diet and continued his remarkably benign course. On the 27th, his serum amylase and WBC count were normal.

On August 28, 26 days post rupture, another barium swallow showed no evidence of extravasation. A fiberoptic esophagoscopy performed one day before discharge revealed the area of the perforation on the left side of the esophagus as a thin fibrous ridge just above a somewhat depressed orange-looking mucosa. No varices or esophagitis was noted.

The patient was discharged on September 7, 1974 in good health.

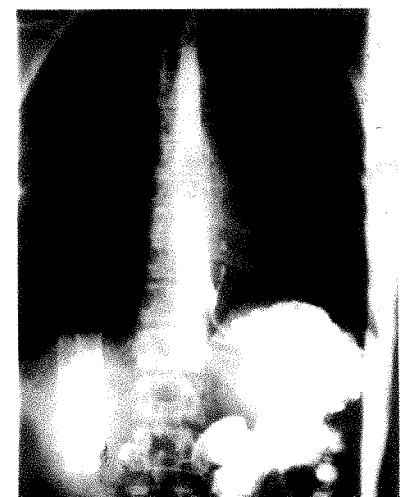


FIG. 4. Barium swallow, 21 days post rupture showing marked improvement since previous study.

Discussion

This patient presented with most of the clinical characteristics of the syndrome described by Hermann Boerhaave in 1724 and subsequently well documented and reviewed in several papers.^{5,6} Classically, the patient is a middle aged, Caucasian male known to indulge in excessive drinking, giving a history of severe retching and vomiting and feeling a sensation of something "snapping" or "giving way" retrosternally followed by excruciating and agonizing pain in the region of the epigastrium. It is reported that swallowing aggravates the pain, and if swallowing is accompanied by coughing, a tear of the mediastinal pleura can be expected. This patient did not give such a history of pain upon swallowing or coughing. The often present and ominous symptoms of respiratory difficulty and vascular collapse, such as dyspnea, cyanosis and shock were not evident in our patient, perhaps as an early sign of the benign clinical course that was to follow.

On physical examination, a critically ill patient is often observed, usually sitting up in bed in a crouched forward position. Subcutaneous emphysema is frequently present as was seen in this patient. Other signs in the chest that are usually present are hydro- or pneumothorax. The abdomen is usually tender, especially in the epigastric region, with varying degrees of rigidity often simulating an intra-abdominal catastrophe.

Among the diagnostic studies, a radiographic examination of the chest usually shows free mediastinal air and hydro- or pneumothorax. At this time the diagnosis should be strongly suspected and contrast examination of the esophagus performed immediately to demonstrate the rent. Esophagoscopy has also been used as a diagnostic tool.^{1,5}

The diagnosis is often missed initially due to the infrequent occurrence of this syndrome and to the many conditions that in some way mimic it. Among these are perforated or bleeding ulcers, acute pancreatitis, acute cholecystitis, myocardial infarction, pulmonary embolism, spontaneous pneumothorax and others.

In 1956, Derbes and Mitchell,⁶ in an extensive and excellent review of this syndrome, reported that out of 55 cases treated by surgery, 36% died, while of 71 medically treated cases 65% died within 24 hours and none lived longer than 7 days.

Bradham, *et al*³ in 1967, wrote, "it is unusual for patients to survive the acute phase of spontaneous perforation of the esophagus without surgical treatment." This

has remained true even at the present time where only sporadic case reports appear where the diagnosis has been missed initially and the patient had survived.^{1,2-4,6,7} Thus the grim prognosis of this entity.

It is unusual and almost unique that a patient with spontaneous rupture of the esophagus would have such a clinically benign course and would not require any kind of surgical treatment such as mediastinal or pleural drainage or thoracotomy.

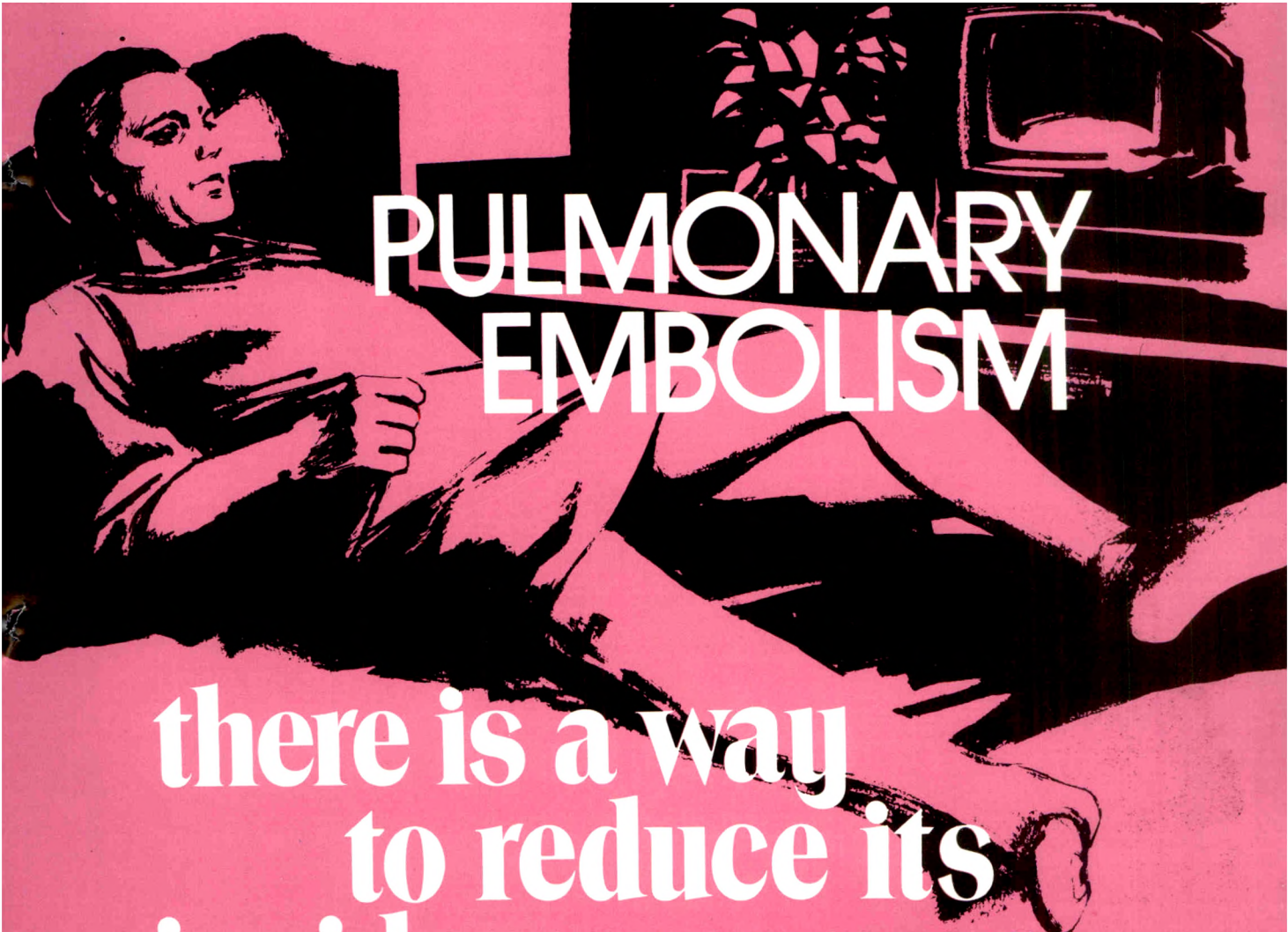
We believe that this patient's unique course was due primarily to non-contamination of the mediastinal and pleural cavities with subsequent free and spontaneous drainage of the extravasated contents into the esophageal lumen. On perforation of the esophagus the spilled contents evoked a localized mediastinal inflammatory reaction which, fortunately, was able to wall-off and contain the spilled matter in an isolated pocket to the left and posterior to the esophagus. This is evident from the roentgen examination of the esophagus, described previously. The fact that an overpenetrated film of the lower thorax, taken 5 hours after a barium swallow, failed to show any extravasated contrast material is further evidence of a communication between the enclosed spilled matter and the esophageal lumen with subsequent spontaneous drainage into the esophagus.

The left pleural effusion observed in this patient was probably a sympathetic reaction secondary to pleural irritation much the same as that secondary to a subphrenic abscess or of acute pancreatitis.

The fact that at the time of perforation his stomach was supposedly relatively empty, plus the coverage with wide spectrum antibiotics may have helped the remarkable recovery of this patient.

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A black and white photograph of a woman lying in a hospital bed, wearing TED anti-embolism stockings. She is looking towards the camera. The background shows a hospital room with a television and some plants.

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to reduce its
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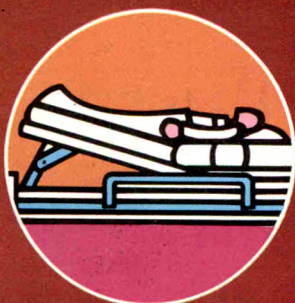
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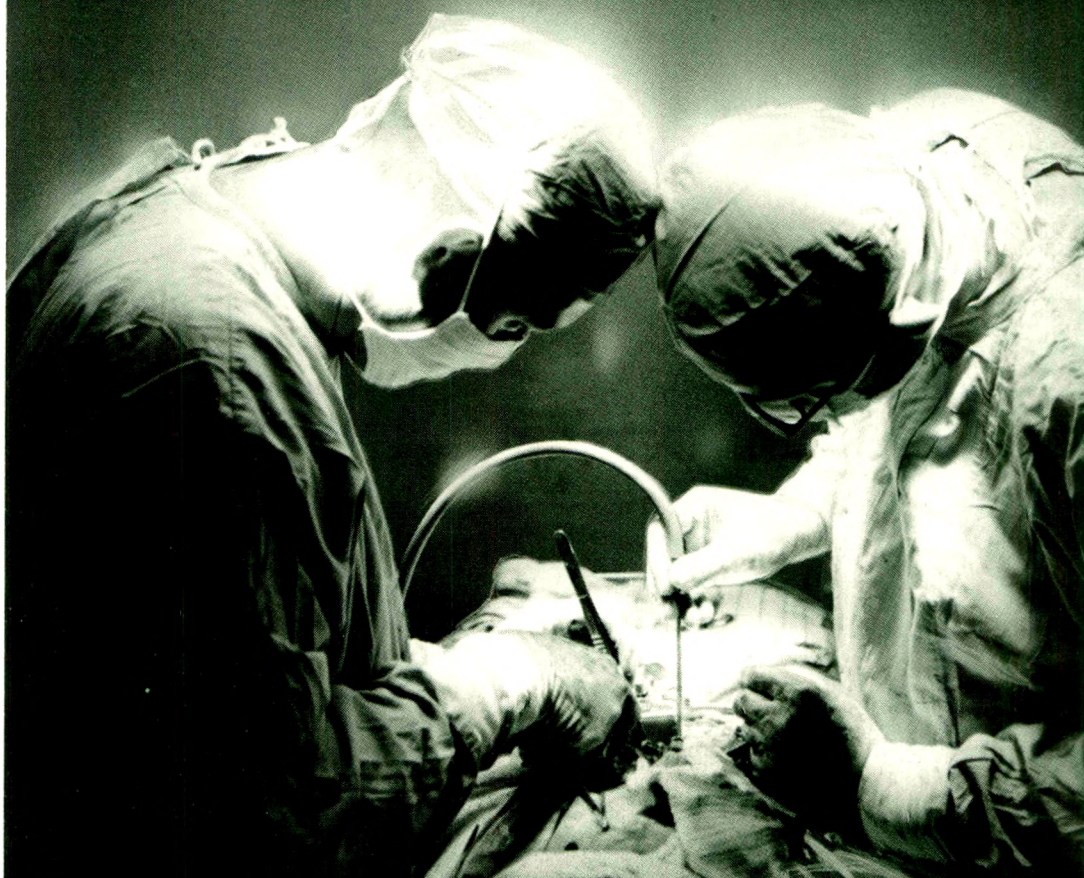
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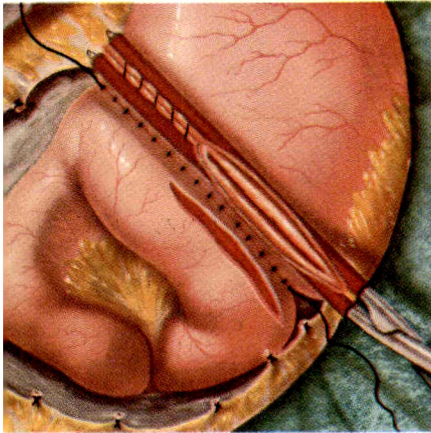
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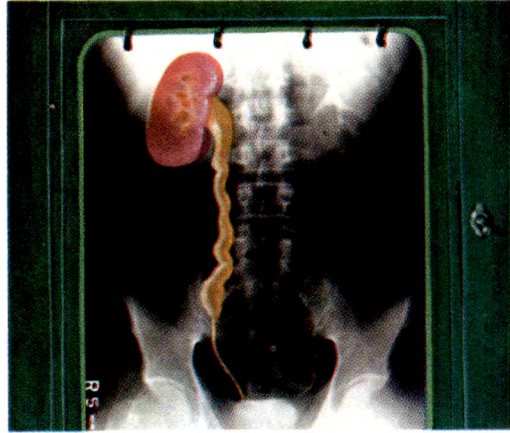
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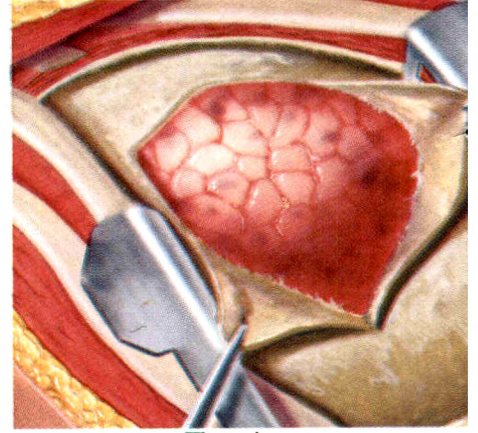
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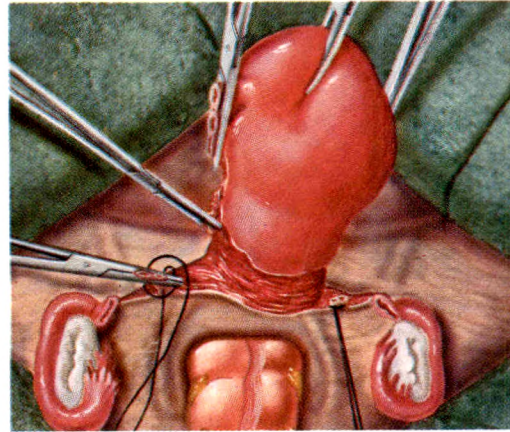
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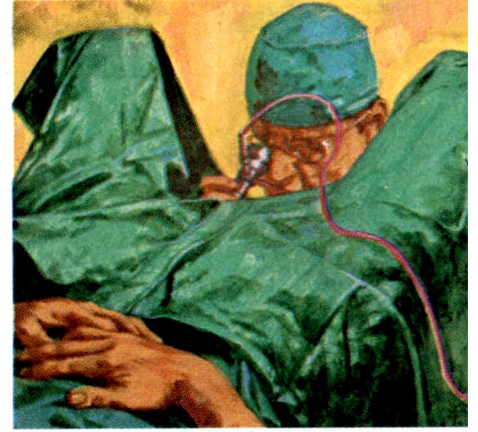
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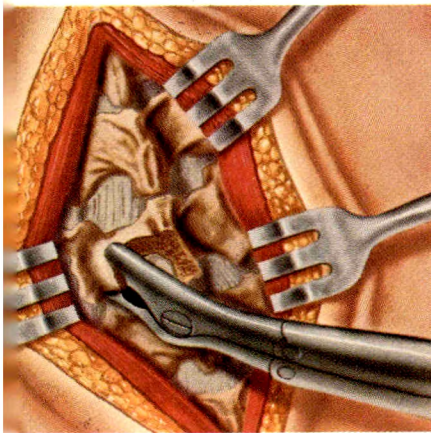
Traumatic pain



Hysterectomy



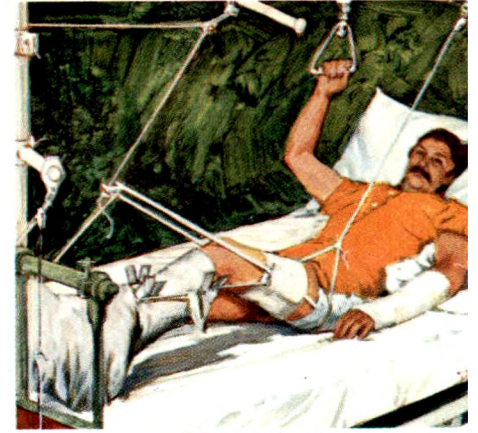
Endoscopy



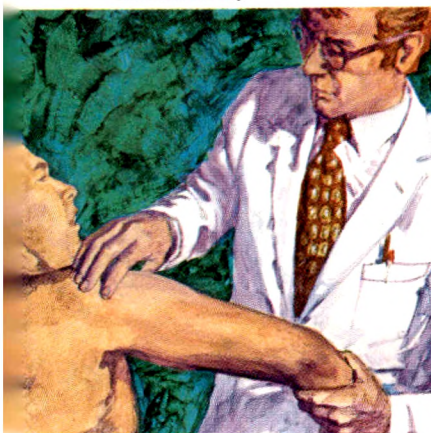
Laminectomy



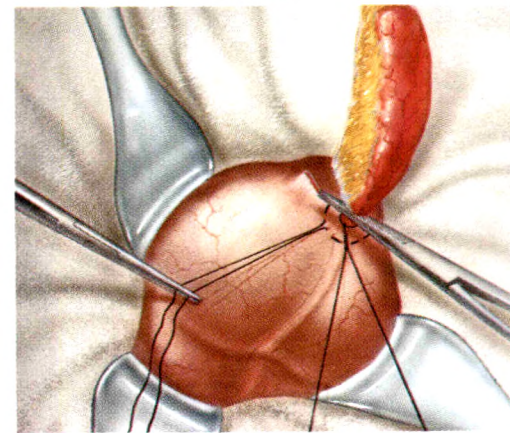
Burns



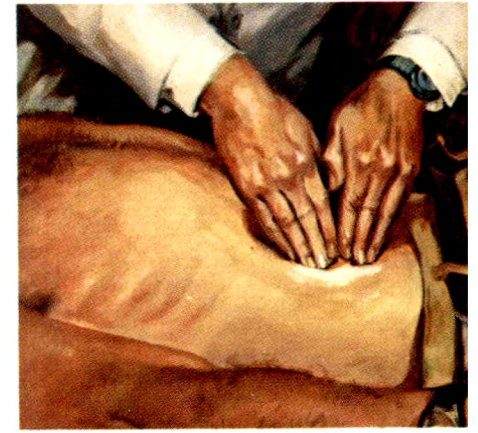
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Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

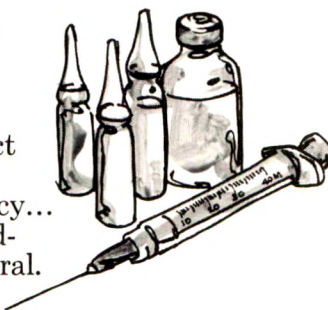
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Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared

spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: Certain Respiratory Conditions. The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis. **Impaired Renal or Hepatic Function.** Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting. **Biliary Surgery.** Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—**respiratory:** respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; **cardiovascular:** circulatory depression, shock, hypertension; **CNS effects:** sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; **gastrointestinal:** constipation, dry mouth; **dermatologic including local:** diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; **other:** urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—**neuromuscular and psychiatric:** muscle tremor, insomnia, disorientation, hallucinations; **gastrointestinal:** taste alteration, diarrhea and cramps; **ophthalmic:** blurred vision, nystagmus, diplopia, miosis; **hematologic:** depression of white blood cells (especially granulocytes), usually reversible and

usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; **dermatologic:** soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; **other:** tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See **Acute CNS Manifestations** and **Drug Dependence** under **WARNINGS**.

Dosage and Administration: Adults, Excluding Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

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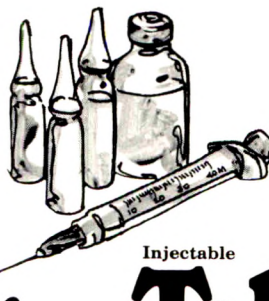
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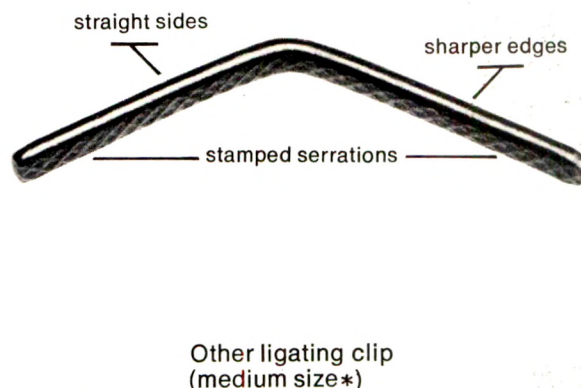
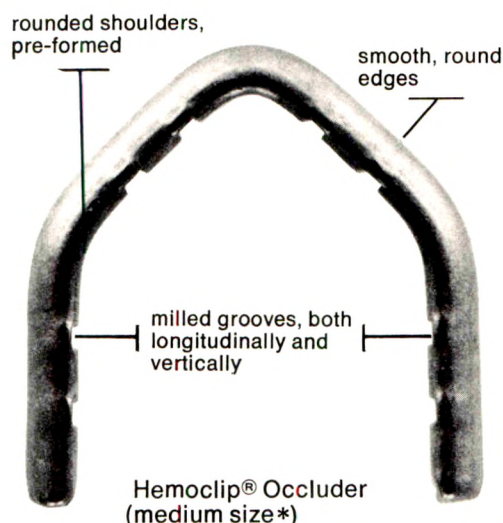


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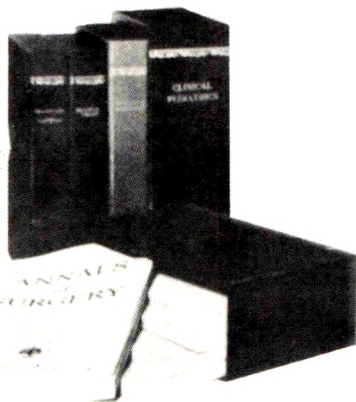
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An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

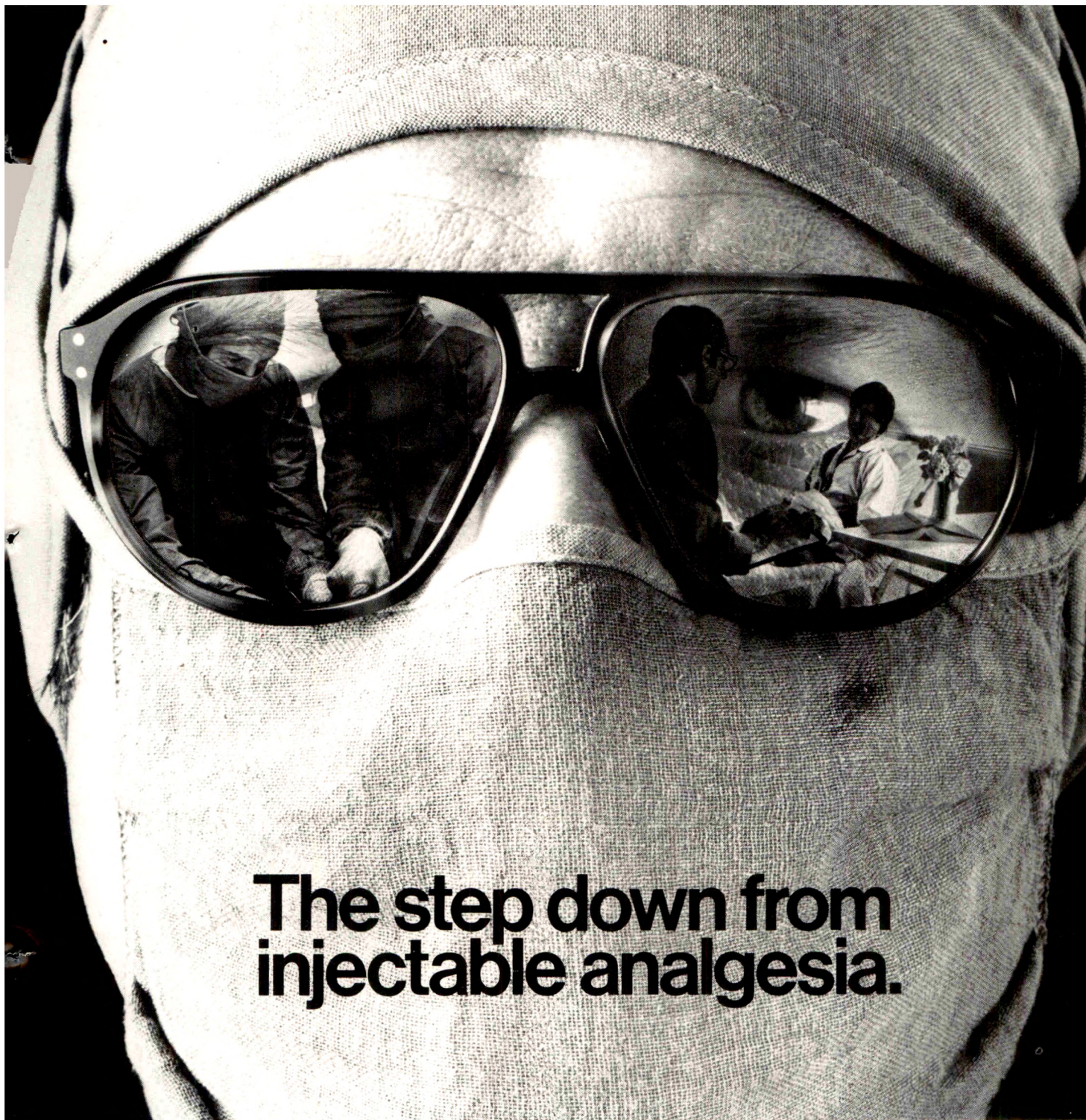
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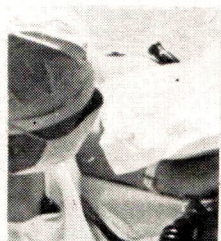
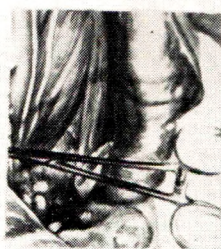
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Marginal Ulcer in Achlorhydric Patients

ROBERT V. TAUXE, LUCIUS F. WRIGHT, M.D., BASIL I. HIRSCHOWITZ, M.D.

Recurrent gastrojejunal ulceration is reported in three patients with histamine-fast achlorhydria. In none of these patients was extruding suture material responsible for the ulceration. However, all three patients had a history of alcohol abuse, and one abused aspirin as well. These cases demonstrate that achlorhydria does not protect against anastomotic ulceration. It is suggested that surgical manipulation produces an increased susceptibility to mucosal damage, and that it is erroneous to consider all anastomotic ulceration as a continuation or recurrence of acid peptic disease.

ULCERATION at the gastrojejunal anastomosis in a patient operated on for peptic ulcer disease is regarded as a recurrent ulcer secondary to inadequate reduction of the secretory capacity of the stomach. Spiro⁹ states that "it is clear that the stomach which is achlorhydric after operation will not lead to an anastomotic ulcer." We report here the details of three cases of endoscopically proven anastomotic ulceration in patients with histamine-fast achlorhydria.

Materials and Methods

In conducting a review of the charts of some 100 patients with endoscopically proven anastomotic ulceration seen at this institution from 1960-1972, we found 3 who had histamine-fast achlorhydria. These 3 patients are the basis for this report.

The endoscopic diagnosis of marginal ulceration was made whenever a clearly defined ulcer crater was seen at the margin or adjacent 1 cm of the stoma.

Gastric analysis was performed by an experienced gastrointestinal secretions technician. The nasogastric tube was placed into the gastric remnant under fluoroscopic guidance. Saliva was expectorated. Basal secretion was

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Department of Medicine, University of
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collected in consecutive 15 minute samples for one hour using continuous low-pressure aspiration supplemented by intermittent syringe suction. Histamine acid phosphate (0.04 mg/kg) was injected subcutaneously after collection of the basal output, and side effects minimized by injection of 20 mg benadryl at the same time. Volume of secretion was recorded to the nearest ml and pH was determined by standardized glass electrode.

Case Reports

CASE 1: A 56-year-old Caucasian man was admitted to University Hospital in January 1971 with a 12 hour history of hematemesis. He was known to have had symptoms of duodenal ulcer disease since 1943 with two episodes of perforation, once in 1947 and again in 1948. In 1948 he underwent a subtotal gastrectomy with Billroth II anastomosis for relief of intractable abdominal pain. In the next 22 years he remained symptom free. The patient suffered a severe burn two years prior to this admission without evident recurrence of ulcer. He had a history of alcohol abuse, but denied excessive ingestion prior to the onset of hematemesis. The only current medication was monthly vitamin B₁₂ injection for pernicious anemia proven by Schilling test. Initial physical exam revealed mild epigastric tenderness. Admission laboratory was normal except for PCV of 35%.

The patient underwent emergency gastroscopy upon admission at which time a bright red adherent clot was observed at the gastrojejunal stoma which was double-barreled.¹ Barium study showed an accumulation on the jejunal side of the anastomosis consistent with a marginal ulcer. After the patient became stable, gastroscopy was repeated and several marginal ulcers were identified in an extremely friable mucosa. The patient had a histamine gastric analysis which demonstrated achlorhydria, with gastric juice pH which was never lower than 6.9 (Table 1).

At the time of surgical revision of the stoma a linear ulceration was found on the surface of a fibrous band separating the afferent from the efferent orifice. The patient was discharged in satisfactory condition on the 22nd hospital day.

CASE 2: The second patient is a 65-year-old Negro man admitted to University Hospital in November 1971 for evaluation of cramping epigastric pain occasionally radiating to the back; starting two years

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Reprint request: Basil I. Hirschowitz, M.D., Director, Division of Gastroenterology, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294.

TABLE 1. Gastric Analysis in Three Patients with Recurrent Ulceration

Sample (15 min intervals)	Case 1		Case 2		Case 3*	
	Output (ml)	pH	Output (ml)	pH	Output (ml)	pH
Fasting	79.0	7.40	57.0	7.20	24.0	6.95
1	19.0	7.25	8.0	7.00	20.0	6.75
2	16.0	7.30	8.0	7.35	16.0	6.79
3	14.0	8.10	4.5	7.50	5.0	7.40
4	7.0	7.60	0.0	—	5.0	6.98
5	12.0	7.45	0.0	—	4.0	7.21
6	10.0	7.75	0.0	—	3.0	7.35
7	20.0	6.90	0.0	—	10.0	6.72
8	26.0	7.25	0.0	—	16.0	6.69
9	—	—	—	—	11.0	6.68
10	—	—	—	—	17.0	7.04

*One of 4 anacid-histamine and 2 insulin studies in the same patient. Histamine acid phosphate 0.04 mg/kg injected subcutaneously after collection of the fourth sample.

after he had undergone subtotal gastrectomy with Billroth II anastomosis for benign gastric ulcer in November 1965. Two months prior to admission the patient had a two week history of hematemesis of sufficient magnitude to reduce the PCV to 25%. The patient had a normal barium study at this time. He also gave a history of alcohol abuse, and a post-traumatic seizure disorder controlled with diphenylhydantoin and phenobarbital. Admission physical examination and laboratory profile were unremarkable. An actively bleeding stomal ulcer was identified by gastroscopy at the time of admission. Histamine gastric analysis revealed achlorhydria with pH of the gastric juice which was never less than 7.0 (Table 1). Because of the achlorhydria, no further surgery was advised and the patient has remained asymptomatic in a further 3 year followup.

CASE 3: The third patient is a 55-year-old Caucasian man admitted to University Hospital in September 1972 for evaluation of postprandial pain, weakness and weight loss. In 1965 he had had a hemigastrectomy and vagotomy with Billroth II anastomosis for a recurrent bleeding duodenal ulcer. In 1966 another bleed was treated by vagotomy. A slowly bleeding marginal ulcer in a double-barrel stoma was diagnosed in 1969 on both gastroscopic and radiologic grounds. Presence of the ulcer was confirmed at operation when the stoma was revised; concurrently a small piece of retained antrum was excised from the duodenal stump. Anacidity was demonstrated prior to the operation by two histamine and two insulin gastric analyses. In 1970 the patient was admitted for control of dumping syndrome. The absence of intrinsic factor was proven by Schilling test (1.7% without and 9% with intrinsic factor) during this admission. In April 1972 gastroscopy again demonstrated the presence of a marginal ulcer. The patient again had histamine-fast achlorhydria. The pH was never less than 6.5. The only medicine the patient was taking at the time of this admission was medium-chain triglycerides used to control steatorrhea. Admission physical exam and laboratory profile were unremarkable.

Gastroscopy was performed twice during this admission showing a marginal ulcer and prolapse of the afferent loop. A third gastroscopy was performed during histamine stimulation. By observation of litmus paper, the pH was never less than 6.5. Bromothymol blue applied to the mucosa after histamine injection indicated that the pH at the mucosa was always greater than 6.0. By glass electrode, three samples of the aspirate had a pH greater than 7.0 in each case.

The patient was treated medically and improved. In January 1974, the patient returned with severe abdominal pain following an alcoholic spree combined with 6-8 aspirin per day. A large stomal ulcer, gastritis, and an afferent-loop ulcer were seen at gastroscopy. Symptomatic improvement followed an antacid regimen. In August 1974 he again had

marginal ulceration seen at endoscopy. He denied intake of both alcohol and aspirin on this occasion. Serum gastrin levels have been consistently less than 50 pg/ml.

Results

A detailed presentation of the gastric analyses on these three patients is given in Table 1. Although there is some fluctuation in both volume and pH, Cases 1 and 2 clearly demonstrated anacidity. In Case 3, the pH was never less than 6.5 and no decrease in pH followed injection of histamine in at least 4 tests; in fact the pH increased during the first 30 minutes.

Two of the three patients had active gastrointestinal bleeding observed at the time of gastroscopy. Two had a long history of anemia, and both had proven pernicious anemia, indicating complete parietal cell atrophy in these cases. Interestingly achlorhydria was present even in the two who had not undergone vagotomy.

It is significant that all 3 patients have a history of alcohol abuse, even though they denied recent excessive consumption prior to their presentation to the hospital. Patient 3, who has had multiple episodes of ulceration had one episode temporally related to a period of heavy drinking and aspirin use. Hence it must be assumed that alcohol was contributory in the development of anastomotic ulceration even in the face of achlorhydria.

Discussion

In an analysis of the gastric secretions of 93 post-gastrectomy patients with recurrent ulceration, Smithwick, Farmer and Harrower⁸ reported that patients with recurrent ulcers always had free hydrochloric acid in their gastric contents, and that no patient with achlorhydria was observed to develop a recurrent ulcer. Scobie and Rovelstad,⁷ in a study of histamine responses in patients with stomal ulcers, found no threshold of acid secretion below which stomal ulcer could be excluded, except for achlorhydria, defined as pH greater than or equal to 7.6. Our experience with these 3 patients leads us to believe that even achlorhydria is not a guarantee against stomal ulceration and leads us to doubt that marginal ulceration is *always* a continuation of the original peptic ulcer disease.

These 3 cases are somewhat analogous to scattered reports in the literature of benign gastric ulcer in patients with histamine fast achlorhydria,^{2,3,5,6,10} including 3 patients with pernicious anemia.^{2,6} In all these patients, acid did not appear to contribute to formation of the ulcer diathesis. It is apparent in our cases that other factors besides gastric acidity may have been involved in the etiology of the recurrent ulcer. Possible causes for ulceration include extruding suture material. We now have seen two patients in whom removal of sutures has led to the closure

of a cutaneous fistula originating from esophagojejunal anastomosis after total gastrectomy, where acid could not be implicated in the pathogenesis. Other possible pathogenetic mechanisms, suggested 25 years ago,⁴ include an increased susceptibility of the anastomosis to break down because of inadequate blood supply resulting from the tight suturing of small bowel vessels at the stoma and clamping of the edges to be anastomosed. Whether other surface-acting agents such as aspirin, alcohol and bile can cause ulceration without such a predisposing state, or even whether they can produce such a lesion at all, remains speculative.

It is likely that endoscopy is allowing diagnosis of marginal ulcer which would previously not have been diagnosed on the basis of x-rays alone, or if suspected from x-ray, would very likely have been considered not present because of achlorhydria. In the future we are, therefore, likely to be seeing more achlorhydric patients with ulcer diagnosed at endoscopy.

In conclusion, our experience suggests that stomal ulceration is frequently a multifactorial disease which occurs because the gastrojejunal stoma has less resistance to damage than does the adjacent unaltered gastric and jejunal mucosa. Thus, caution is advised in considering

further surgical treatment of ulceration without clear evidence of a role for acid in the recurrence in the individual case.

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The Effect of Bile Acid Synthesis on Cholesterol Secretion into the Bile

S. M. STRASBERG* M.D., F.R.C.S. (C), R. G. ILSON B.Sc.

Cholesterol secretion into the bile has been shown to be related to the bile acid secretion rate. It has been suggested that the availability of bile acid micelles controls the entry of cholesterol into the bile. However, previous data could have been interpreted to indicate that bile acid synthesis controls cholesterol secretion into the bile. To discover whether bile acid synthesis has a significant influence on cholesterol secretion, Rhesus monkeys were studied during the period of increasing bile acid secretion and bile acid synthesis, which begins 6-10 hours following interruption of the enterohepatic circulation of bile acids. This is the only condition in which bile acid synthesis and bile acid secretion increase simultaneously. The cholesterol secretion rate fell significantly during this period, and this effect was enhanced by phenobarbital administration. An increasing cholesterol secretion rate would have been expected if micellar attraction controlled cholesterol secretion under these conditions. Bile acid synthesis appears to have an important influence upon cholesterol secretion into the bile.

WHAT MECHANISMS regulate the secretion of cholesterol into the bile? The answer to this unresolved question would probably clarify at least the initial steps in the pathogenesis of cholesterol cholelithiasis and could have significant therapeutic implications in this and other conditions in which cholesterol metabolism may be abnormal.

Studies by Wheeler¹⁸ and Hardison⁶ have demonstrated a relationship between bile acid and cholesterol secretion into the bile. The cholesterol secretion rate (dependent variable) increased as the bile acid secretion rate (independent variable) increased. The rate of increase of the cholesterol secretion rate diminished at higher bile acid secretion rates. Since bile acid micelles solubilize cholesterol in bile, it was suggested that the availability of bile acid micelles was the major factor determining entry of cholesterol into the bile, in these experiments.^{6,18} During a recent study of

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the components of bile flow, sodium taurocholate was infused over 2 weeks at various rates *via* duodenostomy tubes into monkeys with biliary fistulae.¹⁶ Subsequently, the cholesterol, bile acid, and phospholipid concentrations in the bile samples from these animals have been determined, and the secretion rates of these lipids calculated. The results were somewhat different from those previously reported. A large variation in the cholesterol secretion rate was observed at any bile acid secretion rate, in a particular animal. There were significant differences in cholesterol secretion rates between animals with similar bile acid and phospholipid secretion rates (Fig. 1). As in previous studies, and notwithstanding the scatter in the data, there was a significant correlation between the bile acid secretion rate and the cholesterol secretion rate when these parameters were plotted as the independent and dependent variables, respectively. The variation in cholesterol secretion rates, in individual animals, and between animals remains unexplained. However, these findings led us to question whether the bile acid secretion rate really was the independent variable influencing the cholesterol secretion rate. The relationship between cholesterol secretion and bile acid secretion is complex, due to the fact that cholesterol is the precursor of bile acids. It seemed that the data might have been interpreted to indicate that bile acid synthesis, rather than bile acid secretion, significantly influenced cholesterol secretion into the bile. When large amounts of bile acids are returning to the liver from the intestine *via* the portal circulation, high bile acid secretion rates result. Since bile acid synthesis is controlled by feedback inhibition, synthesis is suppressed under these conditions. With less cholesterol being converted to bile acids, there might be more cholesterol available for biliary secretion. The converse could be true at low bile acid secretion rates.

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*Medical Research Council of Canada Scholarship recipient 1973-78.

Cholesterol secretion rates would increase and decrease with the bile acid secretion rates even though the true independent variable was the bile acid synthesis rate.

The present experiment was undertaken to test whether bile acid synthesis has a significant determination upon cholesterol secretion into the bile. One problem in designing such an experiment is that bile acid synthesis and bile acid secretion rates usually vary inversely. Consequently, it is difficult to determine whether an increase in the biliary secretion of cholesterol is related to an increased secretion of bile acids and a greater availability of bile acid micelles, or to diminished bile acid synthesis and increased availability of hepatic cholesterol for biliary secretion. However, starting about 6-10 hours following the total interruption of the enterohepatic circulation of bile acids (EHC), bile acid secretion and synthesis do not vary inversely. Both are increasing and all, or almost all, bile acids secreted into the bile have been newly synthesized in the liver.² Under these conditions, a rising cholesterol secretion rate would favor the micellar availability hypothesis, whereas a falling cholesterol secretion rate would suggest that bile acid synthesis significantly affects cholesterol secretion into the bile.

We have studied the period of increasing bile acid secretion and synthesis which begins several hours following interruption of the EHC, and found that the cholesterol secretion rate decreases during this period. This phenomenon was enhanced by the administration of phenobarbital, a drug known to stimulate bile acid synthesis.¹¹ Cholesterol secretion into the bile appears to be significantly affected by bile acid synthesis.

Methods

I. Experimental Procedure: Three female Rhesus monkeys (4.3-5.0 Kg) were adapted to restraining chairs. At operation, under pentobarbital anesthesia, the supraduodenal common bile duct was cannulated to divert bile flow externally, and the lower cut end of the bile duct was closed with 3-0 chromic sutures. The cystic duct was divided and tied, the gallbladder aspirated (functional cholecystectomy), and a tube duodenostomy was performed.

At least 4 weeks were allowed for recovery. Following the immediate recovery period (5 days), the animals were fed monkey chow 30 gm/kg/day in two daily meals, and given water ad lib. The animals were housed in a room with diurnal variation in lighting. The EHC was maintained by a bile sampler of our own design.¹⁴ No bile samples were taken during this period, so that the EHC was completely intact, except for normal intestinal losses. On the day before the start of an experiment, the bile acid pool was labeled by injection of 5.0 μ Ci ¹⁴C cholic acid (New England Nuclear), into the duodenostomy tube. On the following morning, the EHC was completely interrupted *i.e.* all bile flow was collected. The collection was initiated by posi-

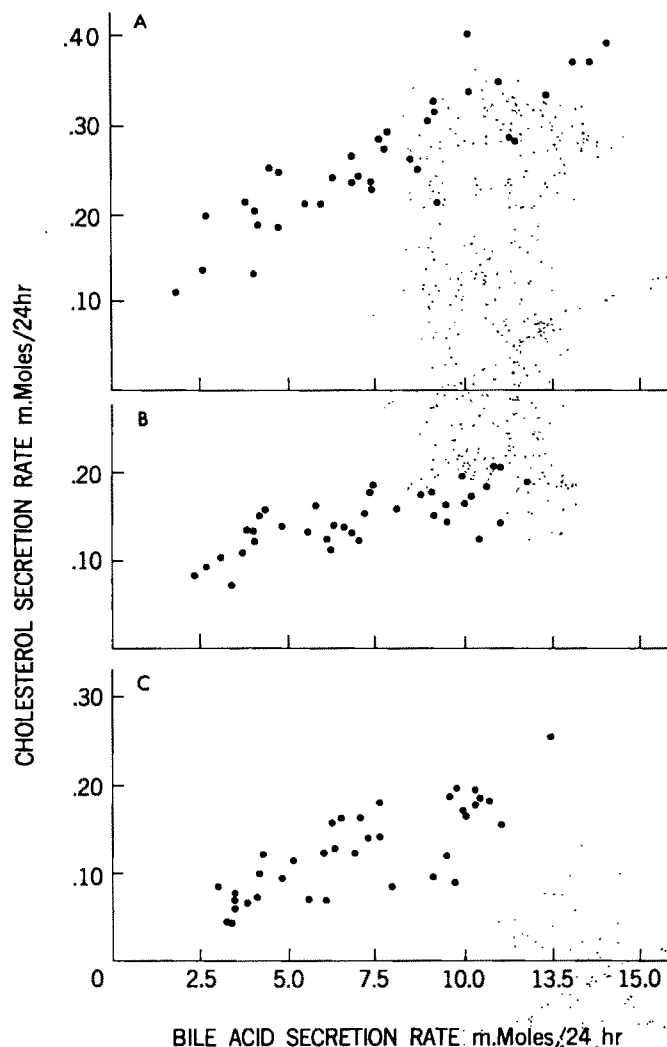


FIG. 1. Bile acid secretion rate vs cholesterol secretion rate, in three animals receiving intraduodenal sodium taurocholate infusions, at various rates over 2 weeks. EHC was totally interrupted. Bile acid secretion rate plotted as independent variable. Correlation coefficients were significant. Note large scatter in data and higher cholesterol secretion rates in animal A. The cholesterol secretion rates were significantly higher in animal A, although there were no differences in bile salt and phospholipid secretion rates among animals. These animals are not the same as those in present study.

tioning the end of the bile duct collecting tube over a fraction collector (Buchler Inst.), and sampling was continued in timed periods for 72 hours. The EHC was then re-established. Two weeks later the experiment was repeated, but for this second study an intravenous infusion of sodium phenobarbital 5 mg/kg/24 hr, in normal saline, was started through a femoral vein catheter 3 days before the interruption and continued throughout the experiment.

One problem in bile sampling is introduced by the bile duct and collecting tube dead space. This problem has been noted by Wheeler.¹⁷ Methods of bile collection which account for dead space errors have been presented by the latter author¹⁷ and ourselves.¹⁵ Unfortunately, these procedures have not been automated, and in an experiment

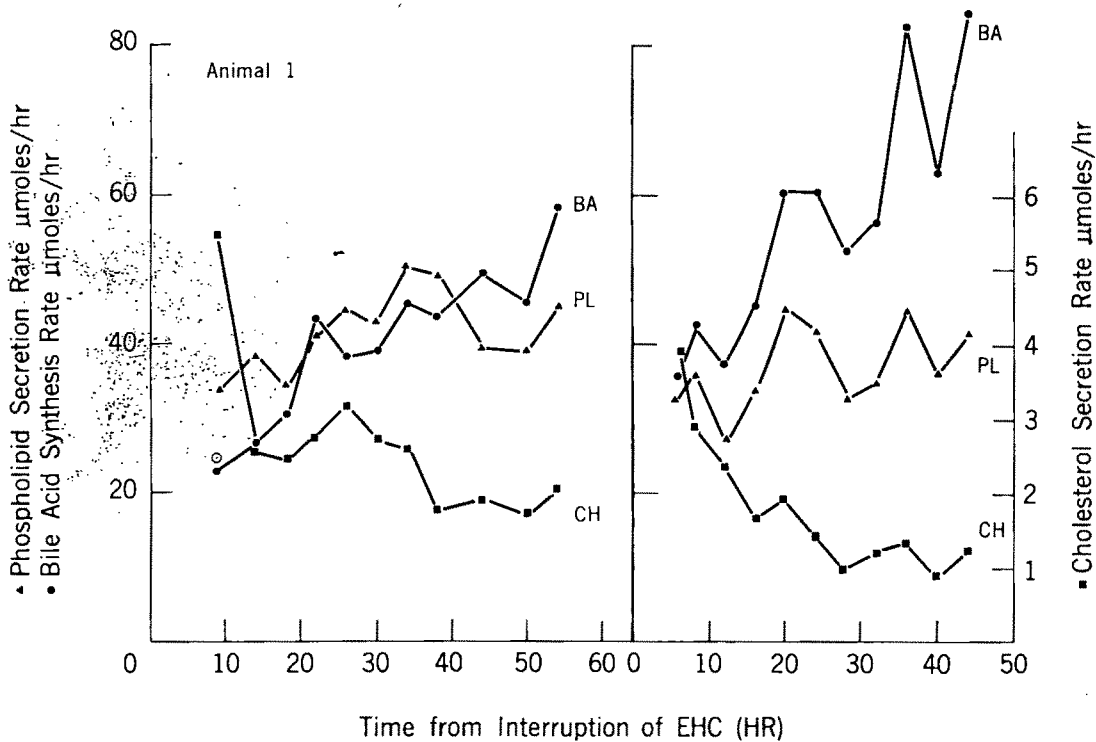


FIG. 2. Bile acid synthesis rates, cholesterol and phospholipid secretion rates vs time. The bile acid synthesis rates were quantitatively identical to the bile acid secretion rates except in the early portions of the studies. When a difference exists the bile acid secretion rate has been plotted as a separate point (circled dot). First portion of experiment is shown on left and second portion (phenobarbital administration) on right. Bile acid synthesis rate cannot be plotted against points for cholesterol secretion rate since a lag exists between stimulus for synthesis and measurable bile acid synthesis determined by secretion of new bile acids into the bile, i.e. a decrease in cholesterol secretion due to entry into bile acid synthesis would precede the measurable increase in synthesis to which the de-

crease in cholesterol secretion is related. Since the events at each point are not synchronous, one can only determine whether there is a significant decrease in cholesterol secretion during the entire period of increasing bile acid synthesis and secretion.

lasting 72 hours they are not applicable. Errors due to dead space are likely to be especially large when two factors are simultaneously present *i.e.* low bile flow and changing bile salt concentrations. When the size of the sample falls to the size of the dead space (approximately 2 ml in this species), a change in the bile acid concentration of 100% from one sample to the next may result in a 100% error in the estimation of the bile acid secretion rate. Both low bile flow and changing bile acid concentrations are commonly present after interruption of the EHC. Sample volumes of 4 ml or less are common when sampling is conducted over hourly periods.³ In the present study, this source of error was minimized by collecting samples of at least 10 ml *i.e.* 5 times the dead space. The volume collected was usually about 15 ml. This reduced the possible maximum error in the estimation of the bile acid secretion rate to approximately 20%, in a case in which the volume collected was 10 ml and the concentration of bile acids in the dead space was twice that of the bile acids actually secreted during the collection period (13% maximum error when 15 ml are collected). The timed periods were usually sufficiently long to collect 10 ml. When less was collected, the sample was pooled with the sample in the next period and the total volume which exceeded 10 ml was treated as a single sample.

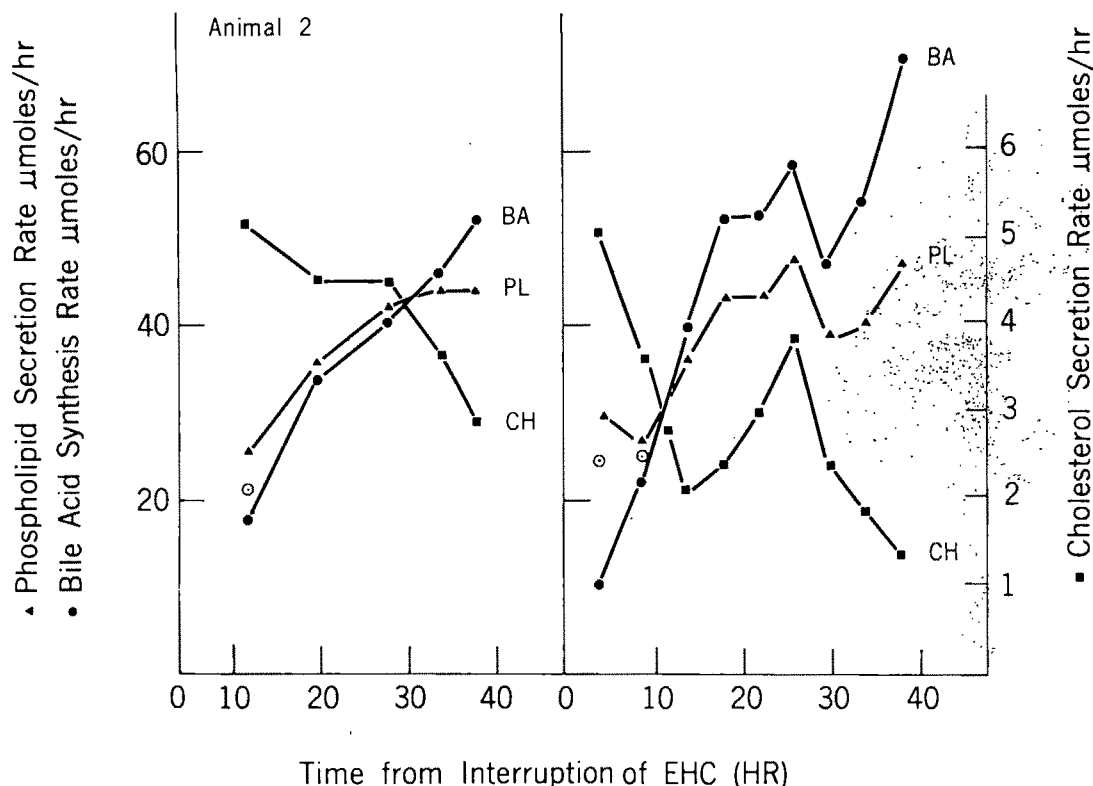
Another possible source of error in this experiment was related to the interpretation of the washout curve of bile

acids following interruption of the EHC. The low point of this curve (bile acid secretion rate vs time) has been interpreted to indicate that point in time at which all the bile acids in the original pool have been washed out. Bile acids secreted into the bile after the low point had been reached were considered to be newly synthesized bile acids.² We have found this to be substantially but not entirely correct. Washout studies, in which the pool has been labeled with radioactive bile acids in this laboratory, suggest that there is a continued secretion of a small amount of bile acids from the original pool for several hours after the low point of the washout curve is reached. The purpose of labeling the pool on the day before the study was to allow for correction of this error so that bile acid secretion and synthesis could be separately measured during this early period of the study. The "specific activity" was calculated as:

$$\frac{\mu\text{Ci (cholic acid)}/\text{ml}}{\mu\text{moles bile acid}/\text{ml}}$$

II. Chemical Analysis: Total bile acid concentration in bile was measured by the enzymatic method,² but the method was modified because of low bile acid concentrations. Two hundred μl of bile were diluted to 10 ml with methanol, as usual. Five hundred μl of the dilution were taken for analysis (rather than 100 μl), dried down under nitrogen, and 100 μl methanol added to redissolve the bile acids. This procedure was performed in the test tube in

FIG. 3. Animal 2 (see Fig. 2).



which the remainder of the reagents were to be added. This modification resulted in the production of a background which was steady, but slightly higher than usual (transmittance before addition of enzyme was reduced to 93-95%). Bile concentrations of cholesterol were measured by a modification of the method by Schoenheimer and Sperry¹² and phospholipid concentrations in bile by the method of Bartlett.¹ Bile samples (200 μ l) were prepared for counting by addition of 17 ml Aquasol (New England Nuclear) and counted, after refrigeration, in a Nuclear Chicago liquid scintillation spectrometer. Internal standardization was performed using 50 μ l ^{14} C toluene (New England Nuclear).

III. Statistical Methods: Linear regression data were computed on an Olivetti P602 calculator using Olivetti programme 1-1 for correlation-regression.

Results

Results are shown in Figs. 2-4. In each experiment the first point shown for bile acid synthesis was obtained from the sample which was at the low point of the washout curve. Whenever the "specific activity" of bile acids in that or any subsequent sample exceeded 5% of the value of the "specific activity" of the first sample obtained after interruption of the EHC, a correction was made to account for the presence of bile acids from the original pool, which were still being "washed out."* Both the bile acid secretion rate and the calculated bile acid synthetic rate are presented for these samples. When the "specific activity" of samples

was less than 5% of the value of the first sample, bile acid synthesis and bile acid secretion rates were taken to be quantitatively identical, and were plotted as one point. When referring to those points in which bile acid synthesis and bile acid secretion rates are identical, the term "bile acid synthesis-secretion rate" will be used. The difference in the number of data points is attributable to collecting samples of a certain volume, instead of collecting over a specific time period. This feature of the experiment probably also accounted for the variation in the timing of the lowpoint of the washout curve, *i.e.* the time of the first sample shown in the graphs. The time shown for each sample in the figures was the midpoint of collection for the sample. For instance, if the bile was collected between 20 and 24 hours after interruption of the EHC, the point was plotted at 22 hours. Between 38 and 56 hours after interruption of the EHC, the bile acid synthesis-secretion rate began to fluctuate slightly below the maximum value obtained to that point. Occasionally, in a subsequent sample during the final 14-34 hours, the bile salt synthesis-secretion rate was slightly greater. The final sample used in the analysis of the data was taken as the one in which the bile

*If the original interpretation of the washout curve were entirely correct, there should be no counts in samples collected after the lowpoint. If chenodeoxycholic acid is washed out differently from cholic acid, a source of error is introduced into the corrections, because of the method of calculation of the "specific activity." This error is almost certainly minor.

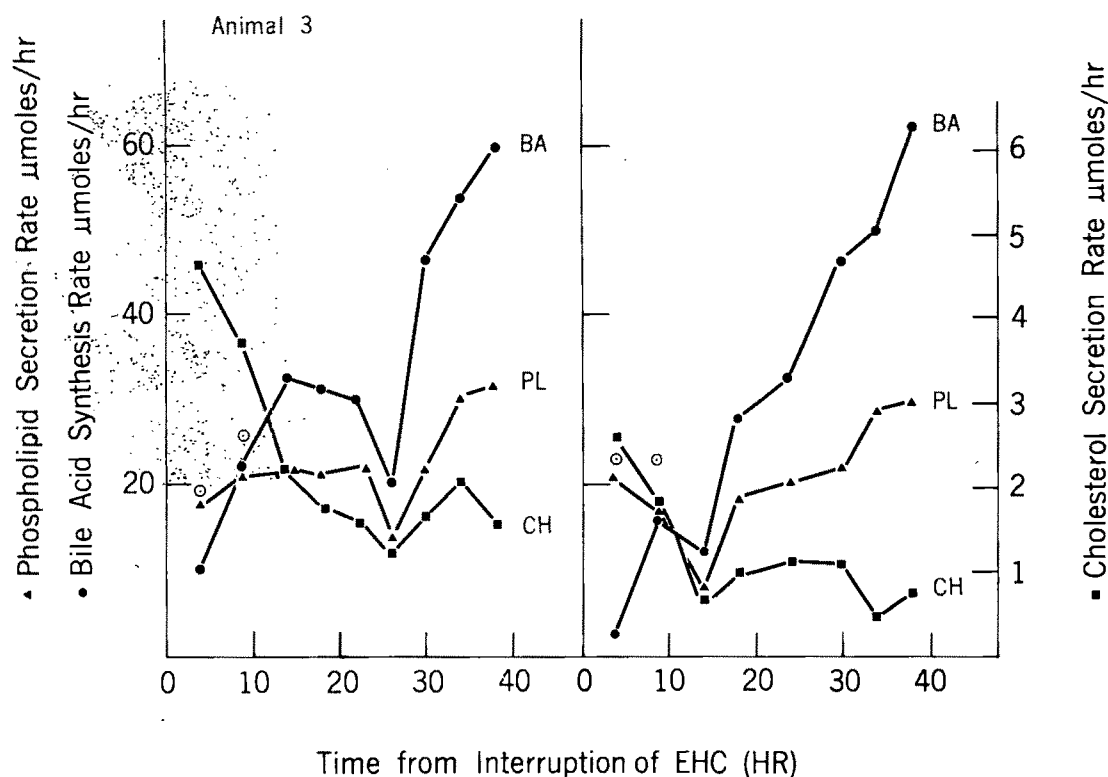


FIG. 4. Animal 3 (see Fig. 2).

acid synthesis-secretion rate was highest, before the curve for bile acid synthesis-secretion rate vs time began to flatten out. The period which was chosen for analysis *i.e.* from the low point of the washout curve to the "maximum" bile acid synthesis-secretion rate was selected because we wished to study cholesterol secretion during the period of simultaneously increasing bile salt secretion rates and bile acid synthesis rates.

The bile acid synthesis-secretion rates increased in every animal, over the period selected for analysis (Table 1, Figs. 2-4). A large decrease in these rates was found in one animal (Fig. 4) in the middle of the period. There was no consistent tendency toward a diurnal variation in synthesis or secretion of bile acids such as has been described for the rat.⁹ The linear correlation data for bile acid synthesis vs time are shown in the table. There was a significant linear correlation coefficient and a positive slope in each case (Table 1). The correlation estimated was for bile acid synthesis vs time rather than bile acid synthesis-secretion vs time since in certain of the early points there was a difference between the synthesis and secretion rates as explained above and in the figures. The slope of the linear regression line is the mean acceleration in bile acid synthesis (mass/time/time). The final rate for bile acid synthesis-secretion, in each animal, was higher in the portions of the experiments in which phenobarbital was infused (Table 1). In one animal this difference was small. The higher final rates observed during phenobarbital infusion were expected from previous reports of the

effect of this drug on bile acid metabolism.¹¹ The acceleration in synthesis (slope) was also greater during phenobarbital infusion, although too few animals were used to prove that this change was significant.

The cholesterol secretion rate decreased in each experiment. The cholesterol secretion rate in the first sample in the study period was not far below the range of normal cholesterol secretion rates in an animal of this species with an intact EHC. This was so despite concomitant bile acid secretion rates which were 5-10% of normal, for this species. There was a significant linear correlation and a negative slope for cholesterol secretion rate vs time (Table 1). The latter indicated that there was a significant decrease in cholesterol secretion during the experiment, but does not imply that the decrease is best described by a straight line. The steepest portion of the curve was usually in the early part of the study. The decrease in the cholesterol secretion rate was small compared to the increase in the bile acid synthesis rate *i.e.* most of the new bile acid was synthesized from cholesterol which was not destined for immediate secretion into the bile. The final cholesterol secretion rates were considerably lower in the second portion of the study, when phenobarbital was administered, than in the first part of the study. Thus the findings were exaggerated by a drug known to stimulate bile acid synthesis. The initial cholesterol secretion rate was also lower, especially in 2 of the 3 animals, so that the total decrease in the cholesterol secretion rate was less, in these 2 animals, in the second

TABLE 1. *Linear Correlation-regression Data for Bile Acid Synthesis Rate and Cholesterol Secretion Rate vs. Time*

	Bile Acid Synthesis Rate vs Time					
	Animal 1		Animal 2		Animal 3	
	Without Phenobarb	With Phenobarb	Without Phenobarb	With Phenobarb	Without Phenobarb	With Phenobarb
n	11	11	5	9	9	8
r	.916	.837	.980	.911	.867	.922
p for r	< 0.001	< 0.001	< 0.01	< 0.001	< 0.01	< 0.01
slope	0.63	0.71	1.25	1.46	1.25	1.67
μ moles/hr/hr						
Bile salt secretion rate of final point	58.3	84.6	52.5	70.8	60.0	62.5
μ moles/hr						
	Cholesterol Secretion Rate vs Time					
	Without Phenobarb	With Phenobarb	Without Phenobarb	With Phenobarb	Without Phenobarb	With Phenobarb
r	-.724	-.860	-.929	-.738	-.782	-.752
p for r	< 0.05	< 0.001	< 0.05	< 0.05	< 0.05	< 0.05
slope	-.058	-.045	-.075	-.075	-.075	-.075
μ moles/hr/hr						
Cholesterol secretion rate of final point	1.70	0.83	2.87	1.37	1.50	0.75
μ moles/hr						

part of the study (see slopes cholesterol secretion rate vs time—Table 1). It seems likely that this was due to an earlier acceleration of the entry rate of cholesterol into bile acid synthesis during phenobarbital administration, rather than a higher basal bile acid synthesis rate. The latter does not appear to have been present (Figs. 2-4), in this experiment. The results for cholesterol secretion in these animals were different from those found in the rat following interruption of the EHC. In that species, cholesterol secretion varied directly and not inversely with the bile acid secretion rate, after interruption of the EHC.⁹

Changes in the phospholipid secretion rate were similar (in direction) to those in the bile acid secretion rate. There was a net increase in the phospholipid secretion rate during the experiment and usually the phospholipid secretion rate followed the smaller increases and decreases in the bile acid synthesis-secretion rate. The increase in the phospholipid secretion rate was not proportional to that in the bile acid synthesis-secretion rate. Phenobarbital seemed to have little effect on the phospholipid secretion rate. In the early stages of the experiment, in which there was a difference between bile acid synthesis and secretion rates, the phospholipid secretion rates appeared to be related to the latter. The connection between phospholipid and bile acid secretion rates is well established.⁸

Discussion

The major findings in this experiment are that cholesterol secretion rates diminish significantly during the period of increasing bile acid synthesis-secretion rates, following interruption of the EHC, and that phenobarbital, a stimulant of bile acid synthesis,¹¹ appears to exag-

gerate these responses to interruption of the EHC. Redinger and Small have already suggested that the decrease in cholesterol secretion into the bile, during phenobarbital administration, is due to increased conversion of cholesterol to bile acids.¹¹ Their studies were conducted in the steady state, with the EHC either completely or partially interrupted. The results of the present experiment strongly suggest that bile acid synthesis has an important influence upon cholesterol secretion into the bile, in normal animals, not receiving drugs. The present experiments do not rule out an action of bile acid secretion upon cholesterol secretion, into the bile. However, during periods of increasing bile acid synthesis, the effect of bile acid secretion on cholesterol secretion is overridden. All bile acid concentrations recorded during the experiment were above (usually many times above) the suggested critical micellar concentration of bile acids in bile⁷ so that this factor could not have accounted for the failure of cholesterol secretion to respond to increasing bile acid secretion. Although this experiment does not exclude an effect of bile acid secretion on cholesterol secretion, neither does it support it. The observation that the cholesterol secretion rate was nearly normal, in each animal, in the early portions of the study, when the bile acid secretion rate was quite low, does raise the question whether bile acid secretion affects cholesterol secretion at all.

There appears to be a limit to the contribution of "biliary destined cholesterol" to bile acid synthesis since the negative slope of the curve of cholesterol secretion vs time decreases in magnitude well before bile acid synthesis reaches a maximum. Indeed, if it did not, cholesterol would disappear completely from the bile.

An experiment in some respects similar to the present

one has been reported by Dowling, Mack and Small.³ In that study, attention was focused on the early portions of the washout curve and few or no samples were taken after 8 hours, in their animals. Our observations were started at about this time. For that reason, and because the sampling methods were different, the results of these two experiments are not comparable. However, the experiments are complementary and the following hypothesis based upon the present experiment may be advanced to explain certain of the findings, in the two studies.

Shortly after the EHC is interrupted the bile acid secretion rate falls precipitously. During this early period, the cholesterol secretion rate declines only slightly. This has been referred to as "uncoupling" of bile acid and cholesterol secretion.³ This term may be inappropriate since as noted above, further evidence will be required to support the hypothesis that bile acid secretion and cholesterol secretion are ever "coupled." A reasonable explanation of the only moderate initial reduction in cholesterol secretion is that there is only moderate diversion of "biliary destined" cholesterol into bile acid synthesis, in this early phase. A reduction in the phospholipid secretion rate is associated with the change in the bile acid secretion rate. The net effect of these changes in biliary lipid secretion is to produce bile which is supersaturated with cholesterol.³

The period of supersaturation is relatively short. Increasing amounts of hepatic cholesterol, at least some of which would have been secreted into the bile, are diverted into bile acid synthesis, and the cholesterol secretion rate falls. The bile acid synthesis-secretion rate increases as the new bile acids are transported, into the bile, after several hours. A more modest increment in the phospholipid secretion rate is associated with the latter. The net result of these changes is the production of bile which is incompletely saturated with cholesterol, once again.

The preceding explanation of events suggests that supersaturation of the bile, following interruption of the EHC, should be more persistent if some factor could be introduced to prevent or retard the onset of bile acid synthesis. One of the authors (S. M. Strasberg with R. H. Egdahl and D. M. Small) had studied such a situation, namely, biliary tract obstruction.¹³ During obstruction there is inhibition of bile acid synthesis, which persists into the post-obstructive period. Interruption of the EHC at the time obstruction is relieved provides the conditions mentioned above. We have studied two animals in this state, and this data was presented in a review article by Redinger and Small.¹⁰ Following a period of partial obstruction in these animals, complete interruption of the EHC resulted in supersaturation of the bile for 16-24 hours, which is considerably longer than in unobstructed animals. The persistent supersaturation of the bile would

seem to be at least partly attributable to a delay in the onset of the conversion of "biliary destined" cholesterol, into bile acids. This may not be the only factor responsible for these findings, since cholesterol synthesis itself is increased during obstruction.⁵ The latter could also make more cholesterol available, for secretion into the bile.

It is not clear from this acute experiment whether the effect of bile acid synthesis on cholesterol secretion into the bile is present in chronic partial interruptions of the EHC. Other compensations for an increase in the bile acid synthesis rate, such as increased cholesterol synthesis, might occur. In the Rhesus monkey, chronic 20% interruption of the EHC resulted in maximal bile acid synthesis rates, normal bile acid secretion rates but no change in the cholesterol secretion rates or relative composition of the bile, when compared to smaller interruptions.³ This suggests that "biliary destined cholesterol" is not affected by large increases in bile acid synthesis, in the chronic state, in this species. Nevertheless, there are suggestions that in man cholesterol secretion rates may be affected by bile acid synthesis rates. Recently, it has been shown that Africans, who eat a diet containing considerable vegetable fiber, have bile acid synthetic rates which are greater than those in "normal" individuals in Western industrialized societies.⁴ The former have gallbladder bile, which is considerably less saturated with cholesterol, than the latter.⁴ The low incidence of cholesterol gallstones in these African tribesmen is likely related to the composition of their gallbladder bile. It seems possible that these individuals may lose larger amounts of bile acid in their stools, and that the increased bile acid synthetic rate, which would occur in response to these increased losses, results in a reduction of cholesterol secretion into the bile. This unproven hypothesis is presently under investigation in our laboratory, since it has potential therapeutic implications, if correct. Addition of fiber, or perhaps low doses of cholestyramine, could result in desaturation of the gallbladder bile. Naturally, the interruption of the EHC would have to be planned to create maximum synthesis, without reducing the bile acid secretion rate, *i.e.* the daily loss induced would have to be less than the maximum synthetic rate.

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Microcirculation of the Normal and Inflamed Canine Pancreas

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Pancreas of normal dogs and the inflamed gland of experimental pancreatitis were studied by intra-arterial injection of Microfil, a silicone-rubber compound especially suited for study of the microcirculation. Duodenal vasculature and lobular vessels of the pancreas were studied as were those supplying the duct. Interlobular vessels were well visualized in the normal pancreas and intralobular vessels formed a fine reticular pattern throughout the cleared lobules. A complex network of vessels in the pancreatic duct was observed using this technique, apparently derived from the interlobular vessels. The blood supply of each layer of the duodenum was evaluated.

Intraductal trypsin injection produced focal areas of pancreatitis associated with edema, poor vascular filling and spastic changes of the lobular vessels. Extravasation of Microfil, although not apparent on normal specimens, was prominent in inflamed specimens and suggested vascular weakness and disruption. Pancreatic lobules adjacent to inflammatory areas showed definite evidence of dilatation. The inflamed pancreatic ducts were markedly edematous, thickened, and showed incomplete vascular filling. When the duodenum adjacent to pancreatitis was injected with Microfil, edema and vasoconstriction were especially prominent in the duodenal muscular layer.

MICROSCOPIC VASCULAR CHANGES in the inflamed pancreas were observed in 1936 by Rich and Duff⁵ to consist of adventitial condensation, swelling of muscle fibers in the media and fraying of the internal elastic lamina. These observations were reported both in human autopsy specimens following hemorrhagic pancreatitis and in experimentally produced pancreatitis in dogs and subsequently, other investigators^{5,8} have published similar reports.

Additional information was published by Thal in 1954,¹⁷ concerning the pancreatic microcirculation following retrograde ductal injection of bile into the rabbit pancreas. Using a transillumination device, he demonstrated segmental spasm of the lobular arteries and veins, with sluggish capillary flow followed within 20

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minutes by capillary rupture and erythrocyte extravasation. Alterations in the pancreatic vasculature following experimental pancreatitis were further quantitated in 1966 by Papp and associates¹⁰ who used radioactive⁸⁶ rubidium to measure decreased pancreatic blood flow rates in bile and trypsin-induced pancreatitis. Redistribution of capillary flow from inflamed to more normal areas in canine trypsin-induced pancreatitis was reported in 1968 by Anderson and Schiller.¹

The following year, Goodhead used radioactive rubidium to demonstrate decreased pancreatic blood flow during bile-trypsin or bile induced pancreatitis.⁶ Studies with mild edematous pancreatitis revealed an increase in pancreatic blood flow apparently secondary to vasodilatation associated with inflammation. A decreased blood flow to the gastrointestinal tract, including the duodenum was also seen with hemorrhagic pancreatitis.

In 1969, Papp and co-workers visualized the microcirculation using intra-arterial injection of either polyvinyl chloride or an india ink-gelatin mixture.¹¹ They found uniform capillary filling in control animals, while poor filling was observed with pancreatitis. There was occlusion of some small arteries with stump-like or pointed terminations and arterial constriction bands were described. In addition, arteriovenous shunting was observed in animals with pancreatitis.

Although these studies contributed valuable data concerning the pancreatic lobular microcirculation, they provided little information concerning changes in the pancreatic ducts and adjacent duodenum. Pathologic changes in these structures are of importance because ductal stricture is reported to be a factor in recurrent pancreatitis and alteration of duodenal motility is commonly observed radiographically.¹⁸

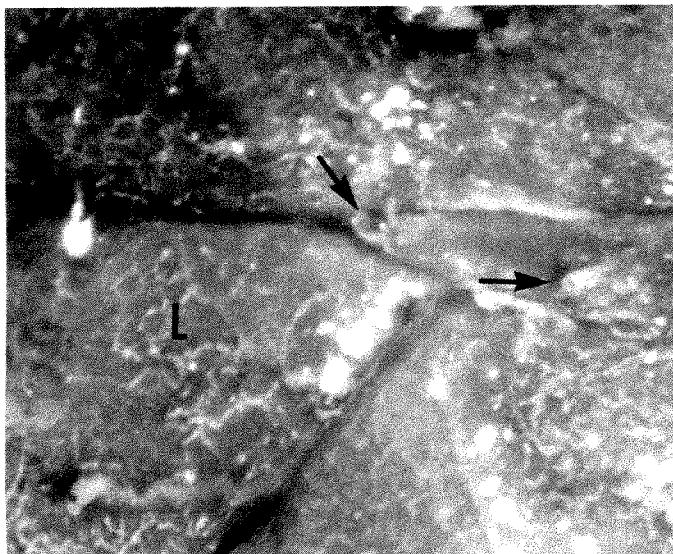


FIG. 1. Dissection microscope view of the cleared, injected pancreas shows several lobules (L) with the typical intralobular vascular pattern. Within the interstitial spaces, larger interlobular vessels are evident (arrows). ($\times 18$)

Material and Methods

Using sterile technique, laparotomy was performed through a midline incision upon 10 anesthetized adult mongrel dogs. In 5 control animals, Microfil, a silicone-rubber compound with a particle size of 1 to 3 microns, was injected under a pressure of 150 mm Hg or less into the cranial pancreaticoduodenal artery according to a technique described by Sobin.¹⁶ The pancreas and adjacent duodenum were immediately excised between clamps and stored in a refrigerator overnight to allow polymerization of the Microfil. Specimens were cut into 10 mm slices, cleared in glycerin solutions graduated

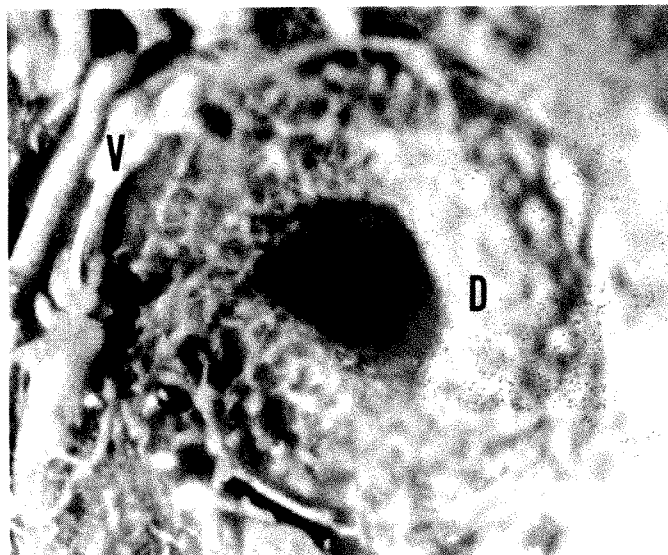


FIG. 3. Proportion of pancreatic duct demonstrates the complex vasculature in the ductal wall (D). The ductal vessels appear to be derived from adjacent interlobular vessels (V). ($\times 18$)

from 75 to 100%, examined with a dissecting microscope and photographed.

In 5 animals, pancreatitis was induced by a transduodenal retrograde injection of 150,000 units of trypsin in 15 ml of saline into the major pancreatic duct, using a controlled pressure of 150 mm Hg. The lesser pancreatic duct was ligated prior to injection and the major pancreatic duct was ligated following injection and the duodenotomy closed in two layers. Twenty-four hours later, the animals were re-operated, Microfil was injected according to the procedure described above, and specimens were obtained and processed.

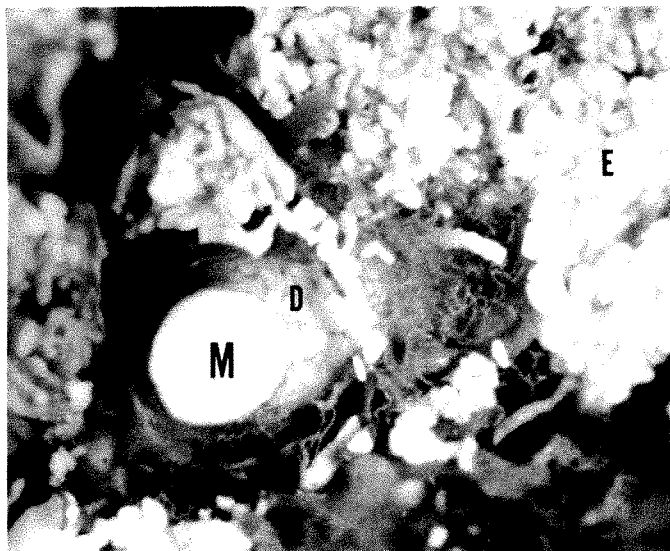


FIG. 2. Preparation was injected sequentially through the pancreatic duct and artery to demonstrate Microfil within the duct lumen (M) and in the surrounding ductal vasculature (D). Intralobular Microfil from the ductal injection is seen in the upper right of the photograph (E). ($\times 18$)

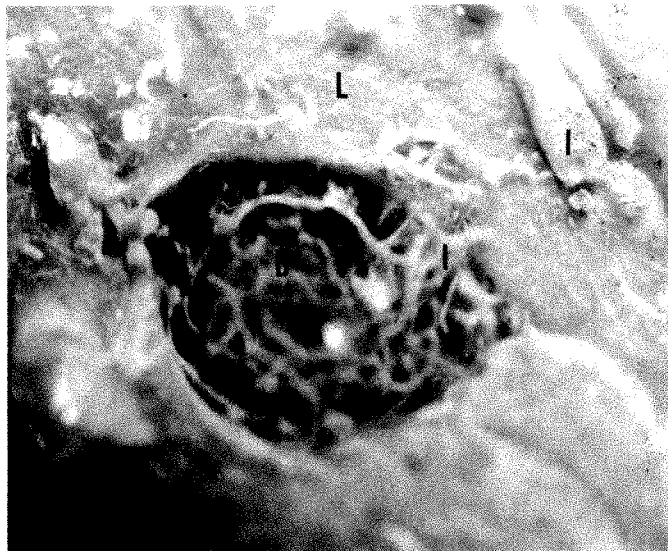


FIG. 4. Small calibre pancreatic duct which shows the ductal vasculature (D) derived from the interlobular vessels (I). The adjacent normal pancreatic lobules (L) are apparent in this preparation. ($\times 18$)

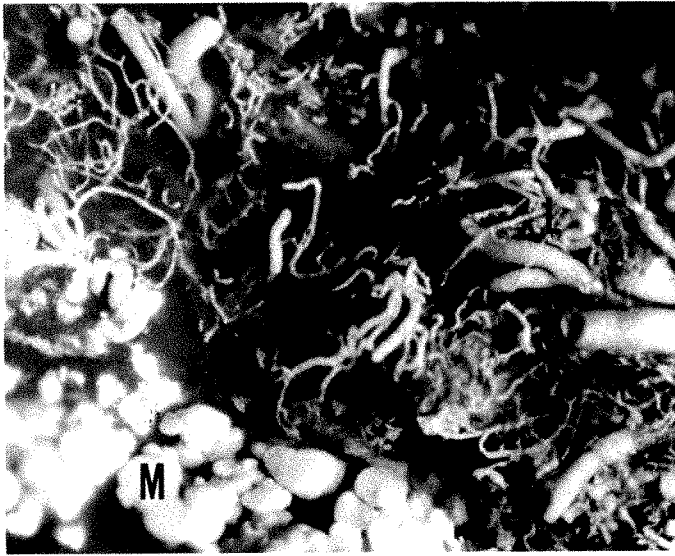


FIG. 5. Following experimental production of acute pancreatitis, injection of this specimen revealed extravasated Microfil (M) suggestive of vascular weakness and disruption. Areas not containing vessels represent edema and there is incomplete filling of vasculature suggesting vasoconstriction. Adjacent areas of pancreas appear to respond by vasodilatation (L). ($\times 18$)

Results

Normal pancreatic lobules were well visualized at low power magnification using the dissecting microscope. The intralobular vessels formed a fine reticular pattern with no evidence of extravasation of contrast material. Larger interlobular vessels were also evident (Fig. 1). When the pancreas was injected with red Microfil in the arteries, after yellow Microfil was injected retrograde into the pancreatic duct, a vascular network was observed surrounding the duct lumen (Fig. 2). Further

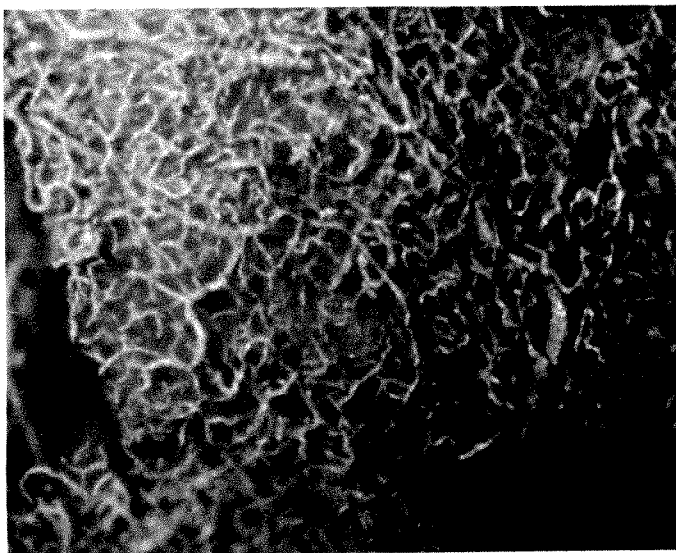


FIG. 6. Areas of pancreas not directly involved by inflammation demonstrate vasodilatation of intralobular vessels as compared to the normal pancreas in Fig. 1. ($\times 18$)



FIG. 7. Vessels in inflamed portions of pancreas often develop beading (short arrows) and pointed terminations (long arrows). Edema is evident and appears to involve the small duct included in this section (D). ($\times 19$)

study revealed that medium sized ducts were endowed with a highly developed vascular supply, apparently derived from interlobular vessels (Fig. 3). The entire wall of the duct was generously supplied by this vascular plexus. Smaller ducts were similarly supplied, although the lumens were more difficult to discern (Fig. 4).

Intraductal trypsin injection produced focal areas of pancreatitis associated with edema and a pronounced tendency for extravasation of contrast material, suggesting vascular damage. Pathologic changes in intralobular vessels were present, with poor vascular filling and apparent fragmentation of vessels (Fig. 5). Normal lobules adjacent to the focal pancreatitis showed evidence of

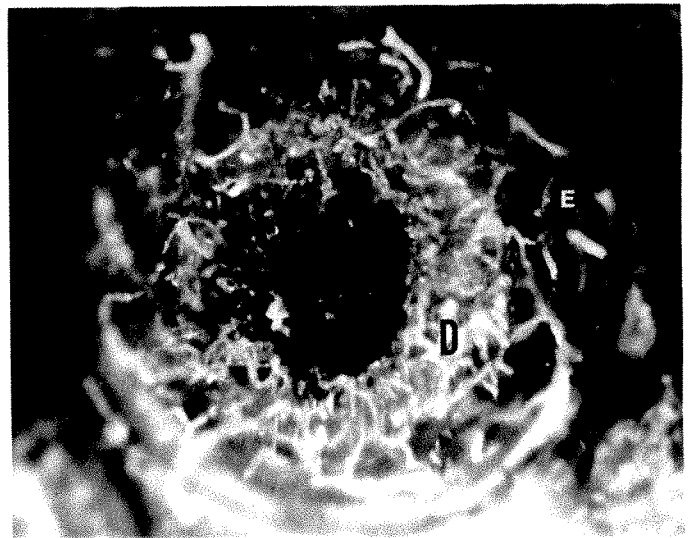


FIG. 8. The duct wall (D) in this section of inflamed pancreas exhibits a striking degree of edema and incomplete vascular filling (E), illustrating the severity of damage to the duct. ($\times 18$)

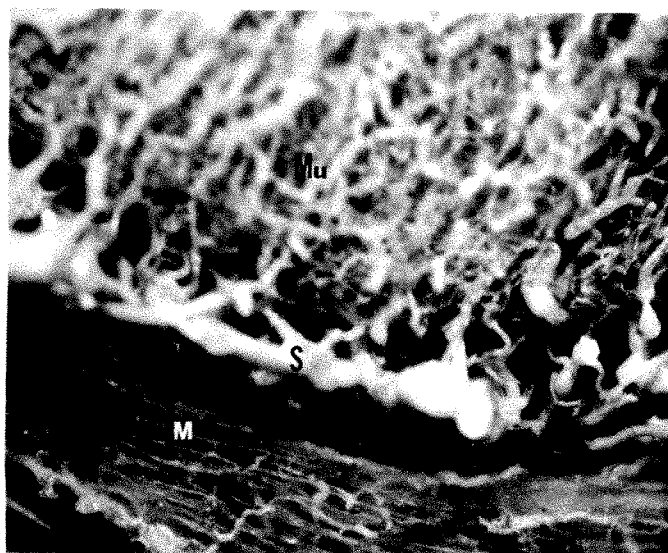


FIG. 9. Microfil injected portion of normal duodenum shows the vascularity of submucosa (S), muscularis (M) and mucosa (Mu). ($\times 18$)

vasodilatation manifested by all vessels which also appeared to be of larger than normal calibre. (Fig. 6).

Pancreatic ducts involved in the inflammatory process showed edema and poor vascular filling of ductal vessels. Some interlobular vessels had pointed terminations while others showed evidence of beading, suggesting vasoconstriction (Fig. 7). Larger ducts involved by the pancreatitis had severe edema in the ductal wall and a definite decrease in vascularity (Fig. 8).

The vascular supply of the normal duodenal muscularis was found to consist of small, closely approximated vessels (Fig. 9). The duodenum adjacent to pancreatic inflammation showed edema of the seromuscular layer along with dilatation and incomplete filling of vessels in the muscularis (Fig. 10).

Discussion

This study demonstrates the focal pattern of edema and vasoconstriction in areas of severe pancreatic inflammation. These observations are especially well seen in the pancreatic lobules and correlate well with those of Goodhead⁶ and Papp and co-workers¹⁰ who studied pancreatic blood flow using radioactive rubidium. As suggested by Popper and associates,¹⁴ this compromise of parenchymal circulation in combination with enzyme extravasation into the gland parenchyma may contribute to increased severity of the pancreatic inflammation. Equally pertinent is the observation that less affected areas seem to develop vasodilatation. These findings suggest that a re-distribution of pancreatic blood flow occurred with hyperperfusion of minimally involved areas and stasis in the inflamed pancreas. These pathologic events were previously observed in 1968 using an india ink injection technique.¹ Most authors agree that

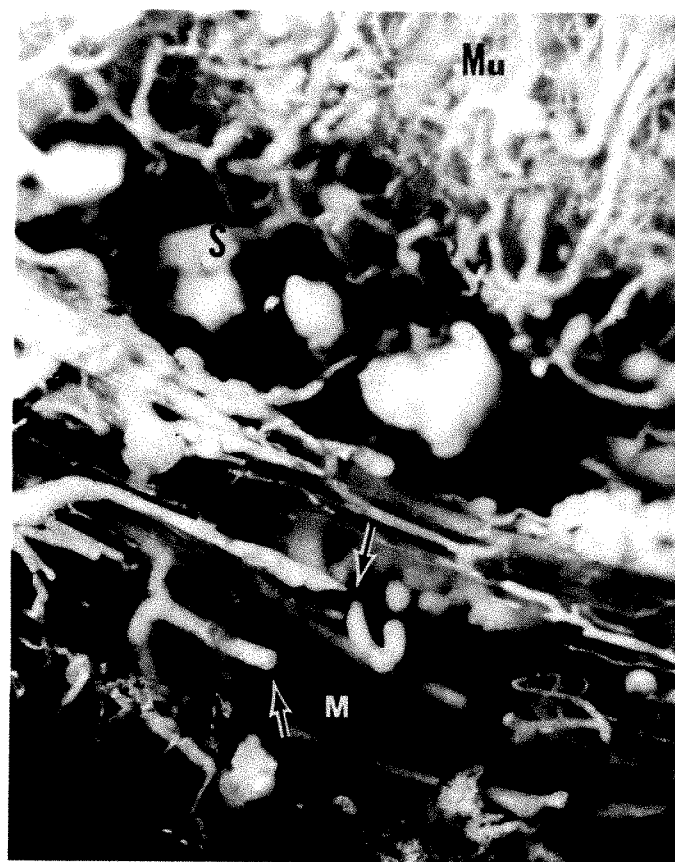


FIG. 10. A portion of duodenum adjacent to uninflamed pancreas shows edema in the muscular layer (M) and vessels in the muscularis exhibit abrupt terminations characteristic of vasoconstriction (arrows). The submucosa (S) and mucosa (Mu) are seen in the upper portion of the photograph. ($\times 22$)

while replacement of fluid losses are of paramount importance in reversing these changes, other adjunctive measures are worthy of consideration.

Further information concerning canine pancreatic blood flow has been published by Delaney and Grim³ who used K^{42} and Rb^{86} clearance techniques. They studied the effects of intravenously administered drugs and found that blood flow was increased by secretin, norepinephrine, and cortisone and decreased by epinephrine and Pitressin. No significant effect was produced by pancreozymin, histamine, dibenzylamine or hypercarbia. These results suggest possible pharmacologic methods of improving pancreatic blood flow. One interesting study by Pissiotis, Condon and Nyhus¹² showed that pancreatitis produced by retrograde ductal injection of an incubated mixture of blood and trypsin resulted in a 40 to 60% decrease in local blood flow. They were able to prevent the blood flow reduction secondary to pancreatitis by an intravenous infusion of vasopressin, although there was no significant effect on normal pancreatic microcirculation. The mechanism of this protective effect of vasopressin observed during pancreatitis was

not well defined. Additional efforts to improve the microcirculation of the inflamed pancreas have been reported⁶ and include administration of heparin and low molecular weight dextran as a means of maintaining patency and flow in small vessels.

Another method of treatment, both experimentally and clinically has been postganglionic sympathetic denervation of the pancreas with the goal of relieving vasospasm and improving pancreatic perfusion. Goodhead and Wright⁷ studied this problem in dogs and found that pancreatic blood flow and perfusion were increased by sympathetic denervation in normal dogs. Furthermore, they concluded that the postganglionic sympathectomy significantly lowered the mortality rate of experimental pancreatitis and prevented the occurrence of severe hemorrhagic pancreatitis as determined by histologic examination. Most of the treated animals developed a milder form of edematous pancreatitis instead of hemorrhagic pancreatitis.

Clinical application of postganglionic sympathectomy as a form of therapy has been published by several authors.^{2,4,9,13} In this small series of patients, the authors reported relief of pain in most and there were some subjective signs of improvement in the course of the disease.

The well developed ductal vasculature seen in this study has not been observed previously in such clear detail. While the present study was not concerned with investigating the precise function of this ductal plexus of vessels, it is interesting to speculate that it is intimately related to the secretory processes of the pancreas. The abnormal vascular filling and edematous changes in the ductal wall secondary to pancreatic inflammation may be responsible for the development of fibrotic ductal strictures in patients with recurrent pancreatitis. Another potentially helpful experimental model might be produced by allowing animals to recover from induced pancreatitis for 30 to 60 days prior to Microfil injection so that the effects of chronicity could be studied. Use of Microfil to inject surgical specimens from humans with chronic pancreatitis also may help to elucidate the relationship of fibrosis to ductal ischemia.

The changes observed in the duodenal microcirculation suggest that the abnormal gastrointestinal motility associated with pancreatitis may result in part from an altered circulation in the duodenal muscularis. This apparent ischemia should be kept in mind when contemplating

duodenotomy in the presence of acute pancreatitis. Poor healing with resultant fistula formation may occur. Although these changes have not been directly visualized previously they are not surprising, since the duodenum and pancreas share a common blood supply. The changes, which may be responsible for long term abnormality, such as ampullary obstruction or chronic abnormalities in duodenal function, deserve further study.

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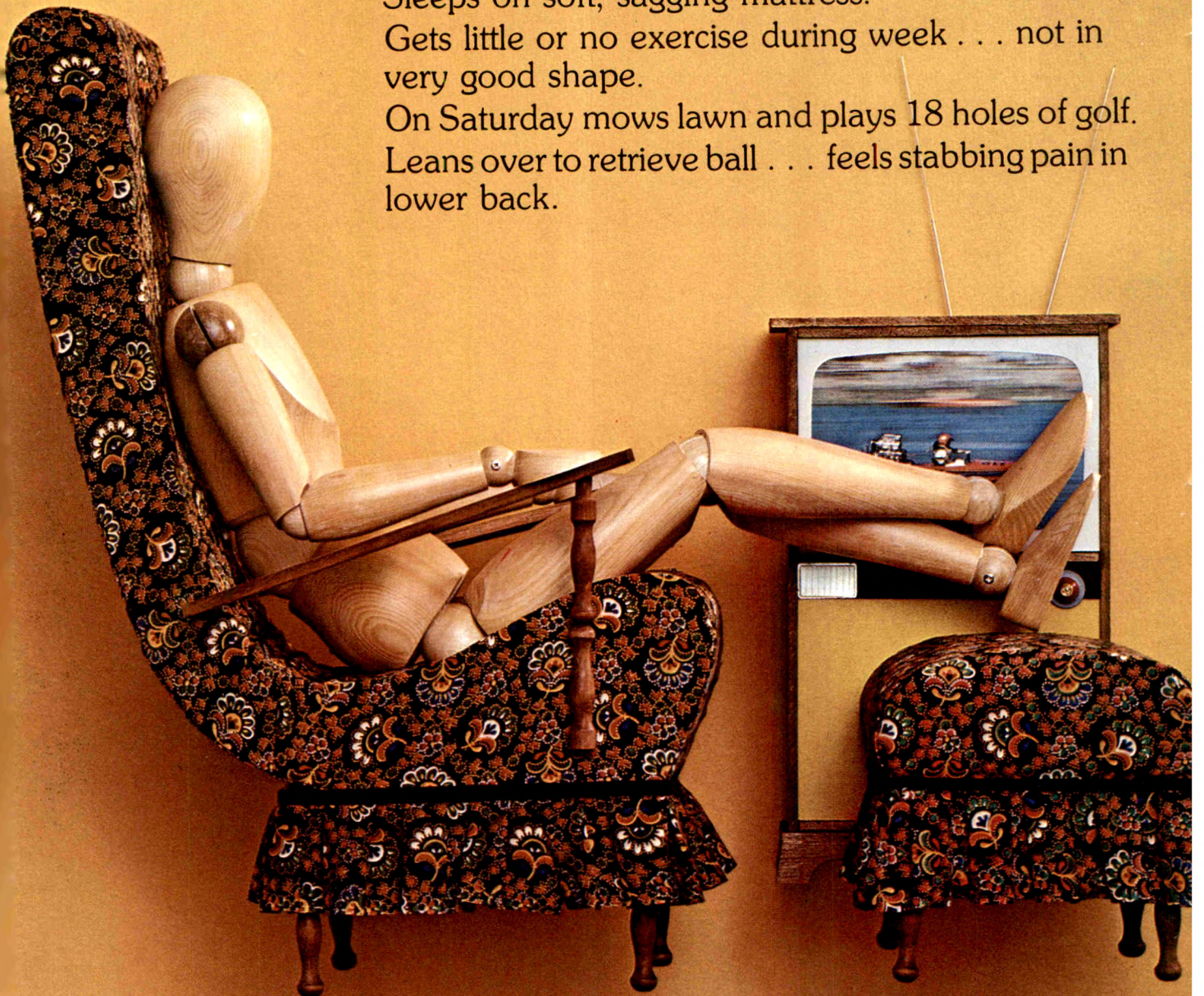
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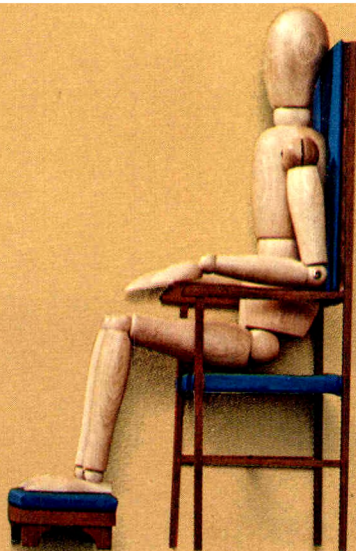
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Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

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Precautions:

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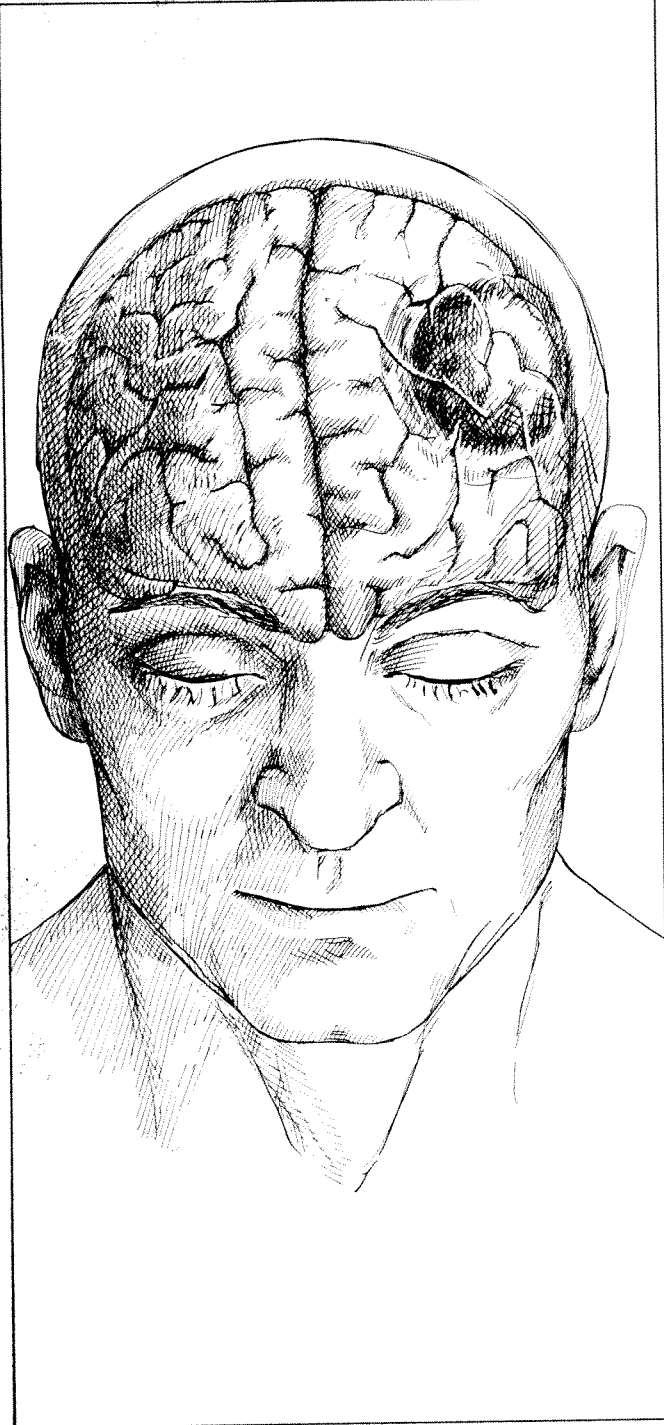
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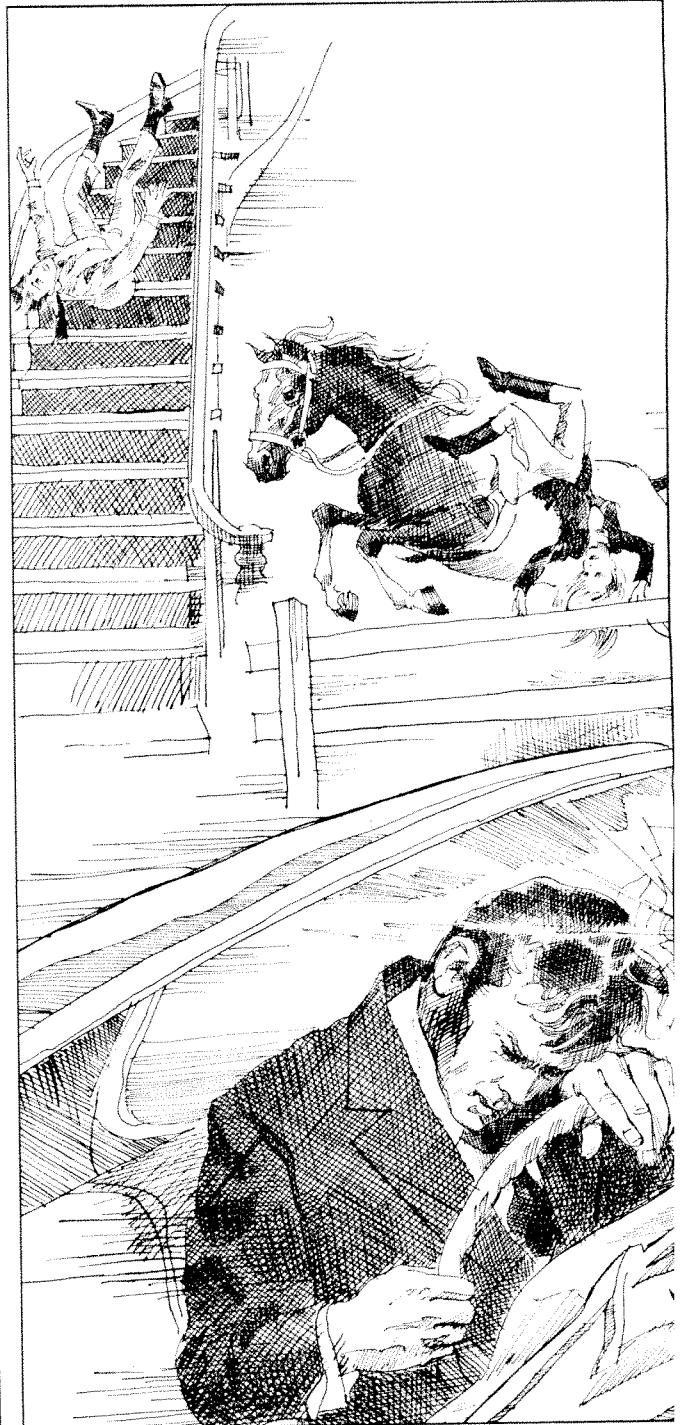
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cerebral

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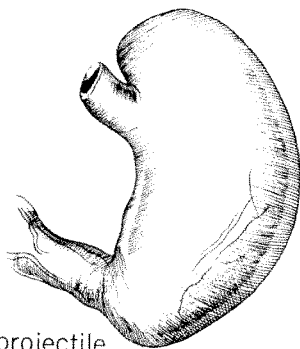


expect it in the presence of severe head injury.

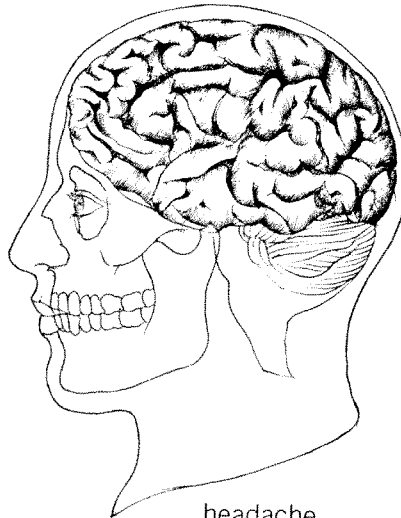


edema*

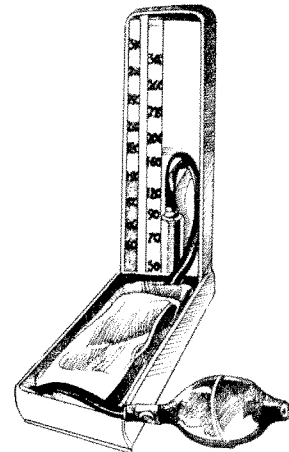
suspect it in the presence
of signs and symptoms such as these:



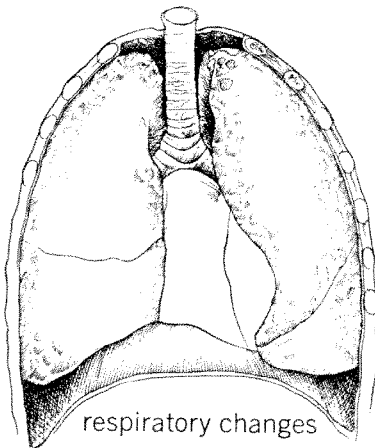
projectile
vomiting



headache,
altered consciousness



increased
blood
pressure

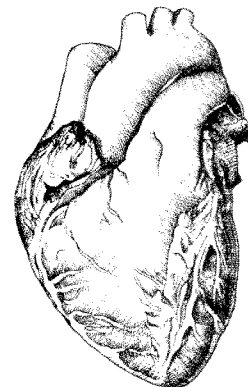


respiratory changes

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papilledema,



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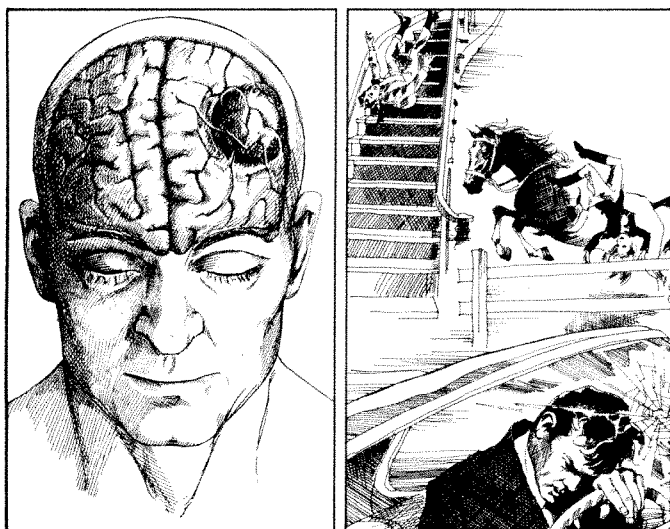
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Ritchie WP: The emergency care of cerebral injuries, J Lancet 86:255, June 1966.

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Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteroids; dietary salt restriction and potassium supplementation may be necessary. All

corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads;

pathologic fracture of long bones. Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

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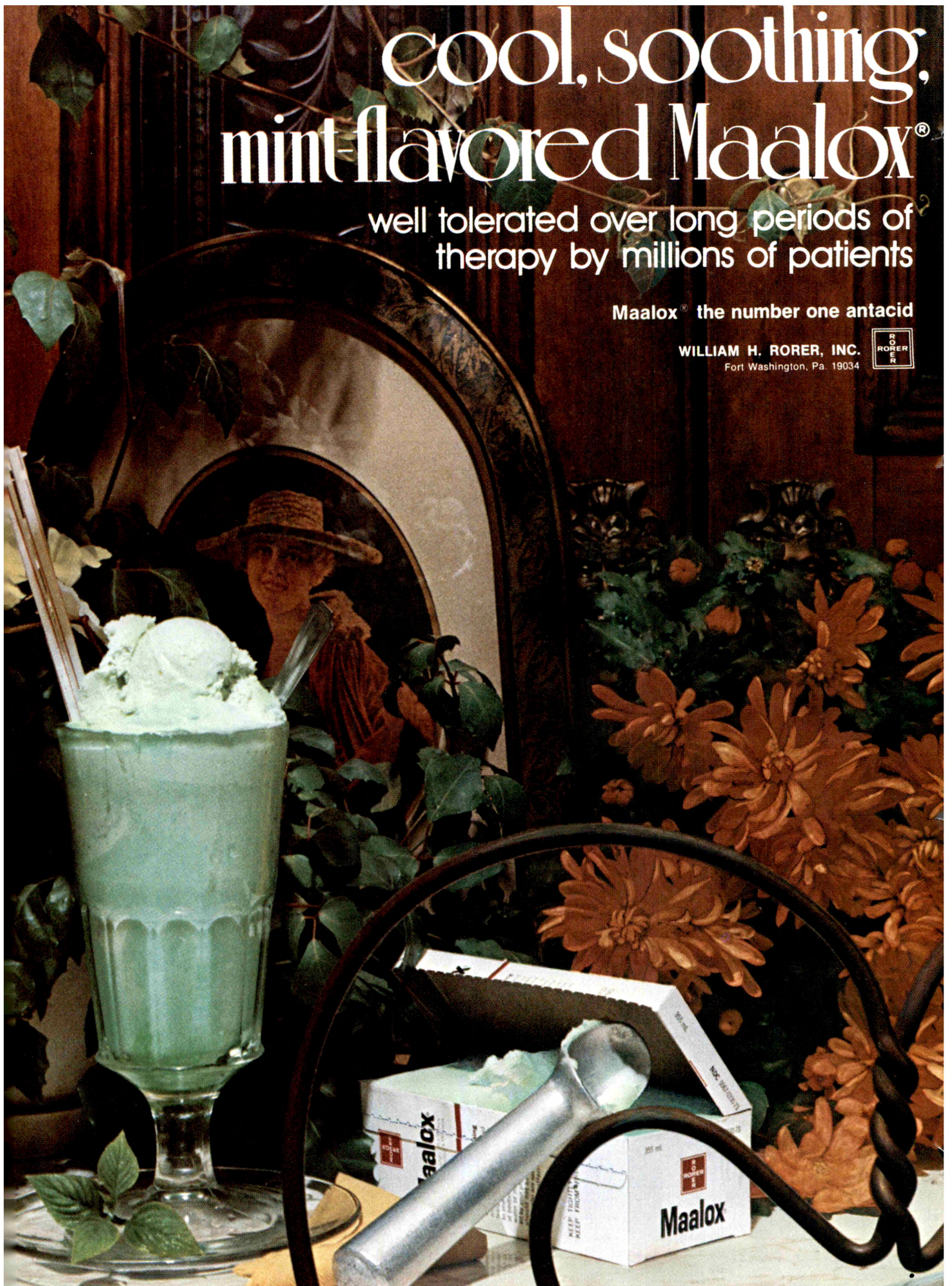
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Renal Cell Carcinoma Presenting as Right Atrial Tumor with Successful Removal Using Cardiopulmonary Bypass

JOY G. PAUL, M.D., DONALD B. RHODES, M.D., & JAMES R. SKOW, M.D.

A 58-year-old male presented with signs and symptoms of right sided heart failure. Diagnostic evaluation revealed a right renal cell carcinoma with extension into the vena cava and right atrium. Surgical management included radical right nephrectomy with retroperitoneal lymph node dissection, inferior vena caval resection, and removal of the intra-atrial tumor thrombus using a cardiopulmonary bypass. Two years after surgery the patient is alive and well with no evidence of recurrent disease.

MASSIVE EXTENSION of renal cell carcinoma into the inferior vena cava represents a surgical challenge. In recent years there have been reports of successful *en bloc* excision of the vena cava,³ removal of large amounts of tumor thrombus extending into the inferior vena cava and right atrium.^{4,5} Our experience with one patient who had a right renal cell carcinoma extending into the vena cava and right atrium prompted this report.

Case Report

A 58-year-old male presented with a two month history of progressive cough, shortness of breath, increasing pedal edema, anorexia, weight loss and progressively enlarging abdominal girth. He denied any hematuria or past history of genitourinary disease. Physical examination revealed tachypnea, jaundice, jugular vein engorgement and bilateral pedal edema. Cardiac auscultation revealed a grade 2/6 systolic murmur heard best in the left parasternal area. The murmur was noted to change in character depending on the patient's position. Examination of the abdomen revealed an enlarged liver and massive ascites.

Laboratory results revealed an elevated alkaline phosphatase, 216 K.A. units, bilirubin of 4.0 mg, and a hematocrit of 63%. His urinalysis showed 2-3 RBC per HPF. Other chemistry results and serum enzymes were normal. Chest x-ray, echocardiogram and cardiac scan revealed a mass lesion in the right atrium. An inferior vena cavogram showed massive venous collaterals as a result of complete obstruction of the inferior vena cava beginning at the level of the iliac veins (Fig. 1). Forward subclavian venogram showed a large filling defect in the right

From the Departments of Surgery, Division of Urology & Cardiovascular Surgery, UCLA School of Medicine, Los Angeles, Ca. and The Santa Barbara Clinic, Santa Barbara, Ca.

atrium (Figure 2a). An abdominal aortogram showed a tumor in the lower pole of the right kidney with neovascularity compatible with carcinoma (Figure 3). Selective celiac and hepatic arteriograms were normal. Liver, bone and lung scans did not reveal metastatic disease.

A laparotomy was performed through a midline incision, extending from the xiphoid to the symphysis pubis. No metastatic tumor was found in the abdominal cavity. Although the liver was enlarged, there was no evidence of metastatic disease. The inferior vena cava was firm and distended with tumor thrombus. Because the kidney and vena cava were felt to be resectable, the incision was extended through the bed of the right fifth rib to the posterior axillary line. A right radical nephrectomy which included Gerota's fascia and a regional lymphadenectomy was performed. The inferior vena cava was mobilized and was transected at the iliac veins and diaphragmatic hiatus. Tumor thrombus could be palpated extending about one centimeter into the left renal vein. This vein was divided distal to the tumor extension and the end of the vein was oversewn. Venous return from the left kidney was maintained through previously established collaterals.

When the pericardium was opened, the right atrium was found to be distended with a firm tumor mass. In order to improve the exposure, the operating table was tilted slightly towards the patient's left. The patient suddenly became hypotensive and ventricular fibrillation occurred. The table was quickly untilted and cardiac massage was started. The fibrillation stopped immediately and he became normotensive. In order to facilitate this aspect of the surgery, the patient was placed on cardiopulmonary bypass using a single venous drainage canula directed from the right atrial appendage into the superior vena cava. Arterial return was via the right common femoral artery.

When the right atrium was opened, the tumor thrombus could be seen extending down the inferior vena cava and obstructing the tricuspid valve. The tumor filled the right atrium and filmy adhesions between the tumor and atrial wall were bluntly dissected. The tumor was separated from the wall of the vena cava, except where it was extending into a hepatic vein. This portion of the tumor could not be removed and was fractured bluntly and left behind. The intracaval and intra-atrial portion of the tumor was then extracted in one piece from the right atrium (Figure 2b). The hepato-duodenal ligament was clamped temporarily to decrease hepatic venous bleeding after the tumor was removed. The

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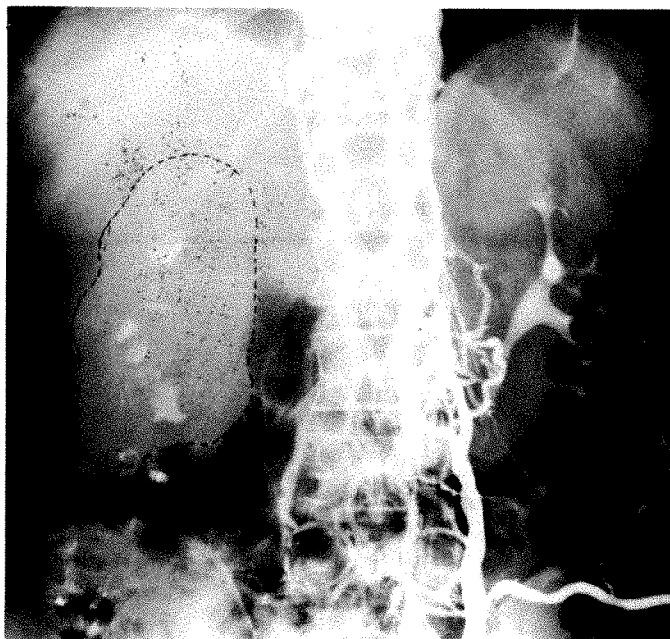


FIG. 1. Inferior venogram showing thrombosis of the inferior vena cava with extensive lumbar collaterals. (Note the distorted calyceal system in the right kidney).

stump of the vena cava just proximal to the hepatic vein was closed with a running suture. The atrium was closed and cardiopulmonary bypass was discontinued.

The patient did surprisingly well postoperatively. His peripheral edema and ascites cleared in the immediate postoperative period. Serum bilirubin rose to 8.5 mg% on the second postoperative day and then gradually returned to normal. Ascitic fluid drained from the wound for approximately 10 days postoperatively and then gradually decreased. The patient was discharged on the 16th postoperative day.

One month later he was readmitted to another hospital with a recurrence of ascites. Over the next several weeks multiple abdominal paracenteses were performed. Subsequently a right subphrenic abscess was discovered and surgically drained. The patient improved quickly and is presently asymptomatic twenty four-months following the first operation and he is leading a normal active life. During the first year he was treated with CCNU* because of the tumor which had been left behind. A complete metastatic work-up at the end of two years showed no evidence of disease.

Discussion

This patient represents one of the many unusual forms of presentation for renal cell carcinoma. An atrial tumor complicated by right heart failure illustrates the need for clearly defining the extension of renal cell carcinoma preoperatively. The value of cavography in detecting tumor extension has been elucidated by Kaufman.² If vena caval involvement is present, and there is evidence suggestive of intra-atrial extension, a cardiopulmonary bypass should be available to facilitate tumor removal with minimal blood loss.

Skinner, *et. al.*,⁴ reported a patient similar to ours in which an intra-atrial extension of renal cell carcinoma was removed by using a vascular clamp to exclude the

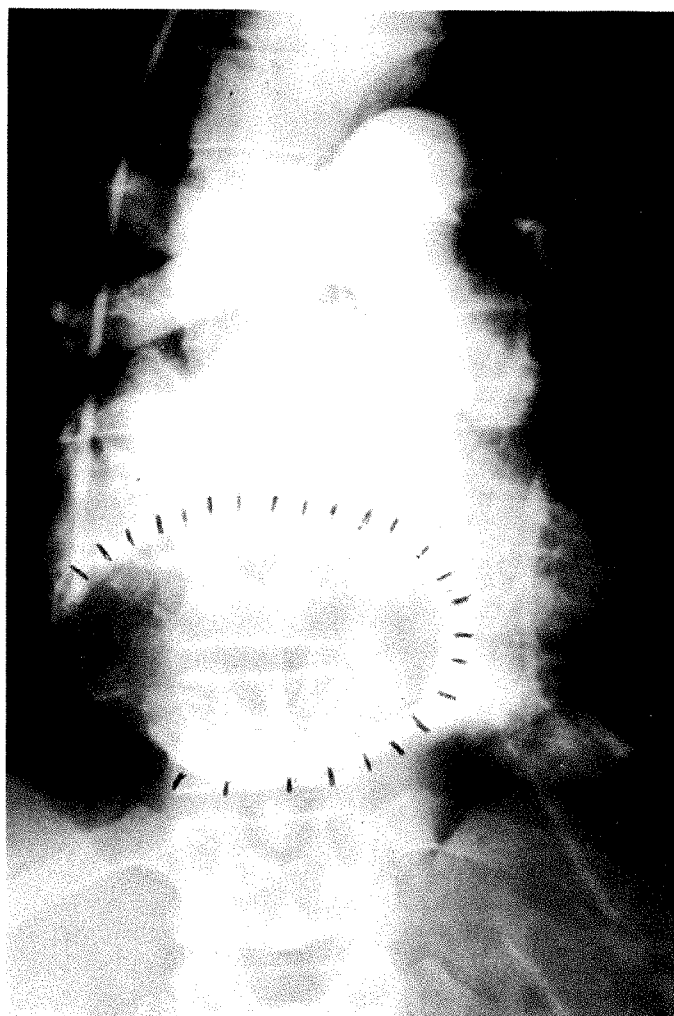


FIG. 2a. Forward subclavian venogram demonstrating large filling defect in the right atrium.

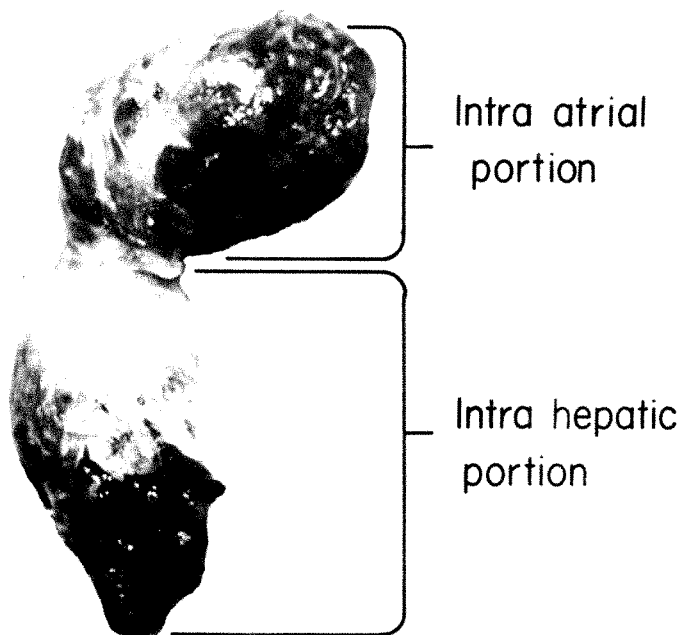


FIG. 2b. Tumor thrombus removed in one piece from the right atrium and intra-hepatic vena cava.

*Cyclo Hexyl Nitroso-urea

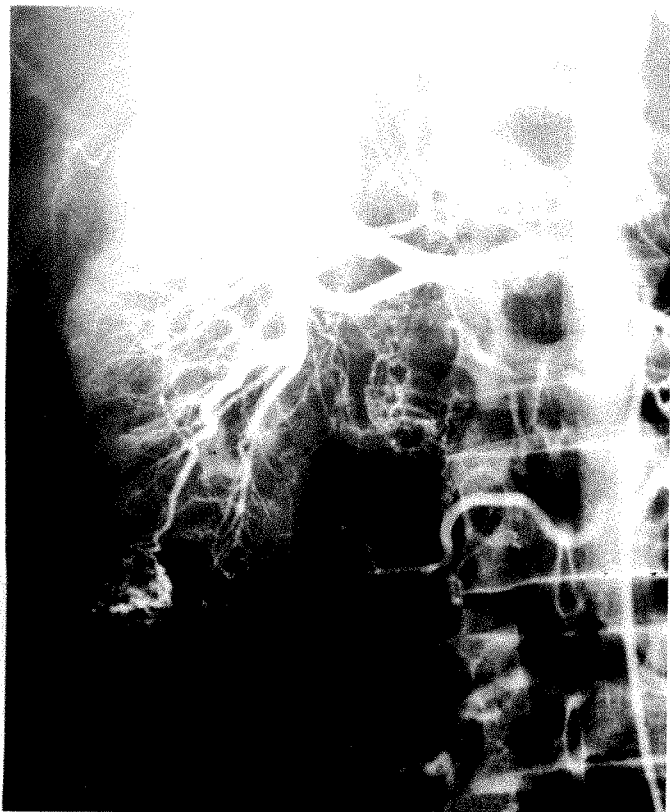


FIG. 3. Right selective Renal Angiogram showing the tumor of the inferior pole of the right kidney.

lower portion of the right atrium and inferior vena cava. Freed¹ described two patients in whom the intra-atrial extension of a tumor thrombus was successfully extracted with the aid of a Foley catheter. We feel that the use of cardiopulmonary bypass is extremely helpful for the removal of a large intra-atrial tumor thrombus particularly when en bloc excision of abdominal vena cava is necessary. Operative blood loss can be minimized by using coronary suction and temporarily clamping the hepatoduodenal ligament with a non-crushing clamp.

Utley, *et al.*,⁵ recently reported a patient with Wilm's tumor who had intra-caval and intra-atrial extension. Their patient became hypotensive following the nephrectomy and closure of the abdomen. The patient's blood pressure was found to be higher when he was lying on his right side. A thoracotomy was performed and the patient

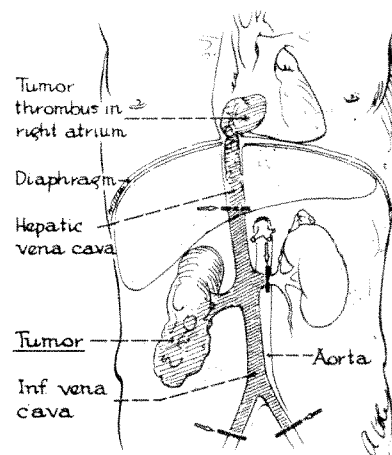


FIG. 4. Diagrammatic representation of operative findings.

was placed on cardiopulmonary bypass, when the right atrium was opened, the tumor was found to be partially occluding the tricuspid valve. A similar situation occurred in our patient when he developed ventricular fibrillation following rotation to the left decubitus position. If a patient is suspected of having tumor extension into the right atrium, the left decubitus position should be avoided until after the patient has been placed on cardiopulmonary bypass.

This patient cannot be considered cured of his carcinoma, but he has led a normal life for 24 months following surgery without clinical evidence of tumor. As improved immunotherapeutic and chemotherapeutic modalities are developed it is likely that the surgical indications for removal of a gross tumor mass will broaden.

Acknowledgment

We would like to thank Stanley A. Brosman, M.D. for his expert assistance in editing.

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Current Management of Upper Gastrointestinal Bleeding

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Over a four-year period, 585 patients were hospitalized for massive upper gastrointestinal bleeding. Endoscopy diagnosed the cause of bleeding in 80% of 200 patients so studied. Selective angiography localized the bleeding site in 12 of 20 patients, and infusion of vasopressor stopped hemorrhage in six. Barium studies were 90% accurate in diagnosing ulcer disease but failed to detect gastritis. One hundred thirty (22%) patients were operated upon for medically uncontrolled bleeding. The proportion of patients requiring surgery fell from 33% in year one to 13% in year four. Benign ulcer disease caused bleeding in 51% of surgical patients, while gastritis was found in 20%, esophageal varices in 15% and stress ulcer in 8%. Overall operative mortality was 29%. Among 38 duodenal ulcer patients, mortality was 18%. Vagotomy and pyloroplasty were more effective than resection in this group. Resection for distal gastric ulcers in 22 patients resulted in a mortality of 14% and no rebleeding. While V&P controlled bleeding in 12 alcoholics with gastritis, five (42%) died postoperatively. Mortality among 20 patients with esophageal varices was 35%, although all five survived who had porto-caval shunts. Eight of 10 patients operated upon for stress ulcer bleeding died. Postoperative rebleeding occurred in 14 patients, eight of whom were again operated upon. In all but one a new lesion was found to be responsible for hemorrhage. Increasing use of gastroscopy and selective angiography can be expected to improve diagnostic capabilities in patients with upper gastrointestinal bleeding. Infusing vasopressor into selected arteries should reduce the need for surgical control of gastritis, variceal and stress ulcer bleeding, conditions poorly managed by current operative techniques.

TECHNIQUES of fiberoptic gastroscopy, selective angiography and intra-arterial infusion of vasopressors expand possibilities in the diagnosis and treatment of massive upper gastrointestinal hemorrhage. Mortality after surgery for such bleeding remains high despite greater selectivity in the choice of operation.

This is a review of our experience in diagnosing and treating upper gastrointestinal bleeding at a municipal hospital over a period of years coinciding with the development and use of fiberoptic gastroscopy and angiog-

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raphy. This period was a transition between the past era of utilizing one operation for the control of upper gastrointestinal bleeding and the present era of tailoring procedures to the specific conditions causing hemorrhage.

Methods and Materials

During the four years, 1969 through 1973, a total of 585 patients with acute upper gastrointestinal bleeding were treated in the Denver General Hospital. Such patients comprised 1.1–1.2% of all hospitalizations during each year of the study.

The diagnosis of upper gastrointestinal hemorrhage was based upon evidence of hematemesis or recovery of blood from the stomach. Initial treatment under the combined direction of both medical and surgical services consisted of cold saline irrigation of the stomach via a nasogastric tube and intravenous administration of crystalloid solutions. Whole blood was transfused when shed blood exceeded one liter in volume, when systolic blood pressure fell from normal to below 80 mmHg or when the hematocrit was less than 30%.

Fiberoptic Gastroscopy

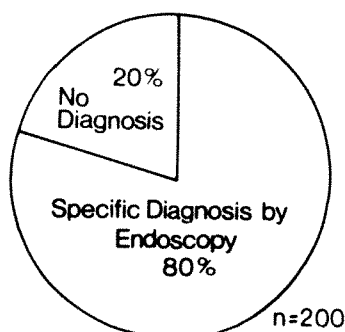
A fiberoptic gastroduodenoscope was used to locate the site of active bleeding in 200 patients. A completely accurate diagnosis, as confirmed by gastrotomy, barium studies, subsequent elective gastroscopy or autopsy, was made in 80% of these patients (Fig. 1).

Among 50 consecutive bleeders endoscoped during year four of the study, an actively bleeding lesion was identified in 46 (92%). More than half (55%) of this group had two or more potential bleeding sites. Erosive gastritis was seen in 31, gastric ulcer in 17, esophageal varices in 12, esophagitis in eight, duodenal ulcer in five and Mallory-Weiss lesions of esophageal mucosa in five patients.

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FIG. 1. Fiberoptic gastroduodenoscopy provided a specific diagnosis of the cause of acute upper gastrointestinal bleeding in 160 of 200 patients (80%).



During the first two years of study, occasional patients were examined with the gastroduodenoscope while massively bleeding. This proved frustrating and unrewarding. Subsequently, gastroscopy was performed only after profuse bleeding subsided, usually within 12 hours following hospitalization.

Selective Angiography

During the final study year (1973), 20 patients underwent selective angiography to determine the site of upper gastrointestinal hemorrhage. Catheters were introduced via the femoral artery in all but one patient. Attempts to enter the left gastric artery were unsuccessful in three patients.

A precise diagnosis was established in 12 (60%) patients (Fig. 2). Five had esophageal varices demonstrated without obvious loss of contrast media into the esophageal lumen. Subsequent findings confirmed that these patients had no other cause of bleeding. Gastric ulcers were diagnosed in two patients and multiple bleeding sites, typical of stress ulceration, in two others. Alcoholic gastritis and a Mallory-Weiss esophageal tear were found in one patient each.

In two patients, angiography demonstrated esophageal varices but gastroscopy revealed other potential bleeding sites.

A cause of bleeding was not established in six other patients with angiographic techniques. Four of these patients had stopped bleeding by the time contrast media was injected. One patient bleeding from stress ulcers and

FIG. 2. Selective angiography provided a specific diagnosis of the site of bleeding in 12 of 20 patients (60%).

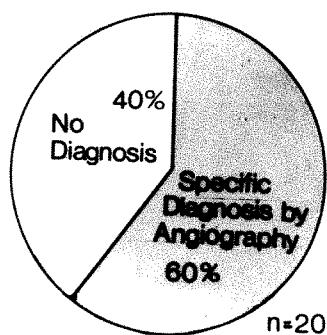
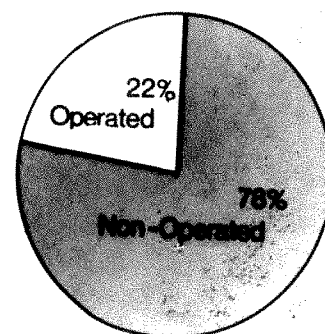


FIG. 3. Of 585 patients with acute upper gastrointestinal hemorrhage, 130 (22%) required operation.



another bleeding from gastric ulcer were not diagnosed by angiography.

Of the 20 patients studied, one developed a hematoma at the site of femoral artery catheterization and one required removal of the catheter because of arterial spasm.

Intra-arterial Infusion

With intra-arterial catheters selectively placed, vasopressin, 0.2-0.4 units per minute, was infused in 12 patients to control active hemorrhage. Bleeding stopped in six patients (50%) within 90 minutes of beginning infusion. Two of these patients had esophageal variceal hemorrhage. Two others had gastric ulcers. One patient with alcoholic gastritis and another with multiple stress ulcers responded to infusion.

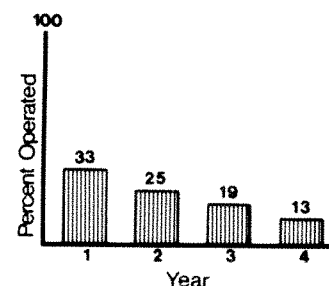
A patient with gastritis had stopped bleeding after infusion was begun but rebled when the catheter was removed accidentally five hours later.

Five patients did not respond to infusion of vasopressor and required operation. Two were bleeding from varices, two from stress ulcers and one from gastritis. In neither of the stress ulcer patients was the left gastric artery catheterized successfully.

Barium Roentgenographic Studies

In only 11 patients (1.9%) was the exact cause of bleeding diagnosed during active hemorrhage by means of barium swallow or upper gastrointestinal series alone. Barium studies were obtained routinely in most patients after bleeding stopped. Peptic ulcer disease was diag-

FIG. 4. The proportion of bleeding patients requiring surgery fell progressively from year one (33%) through year four (13%) of the study.



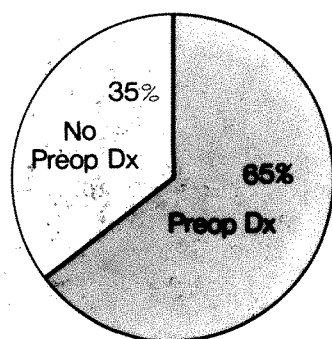


FIG. 5. A preoperative diagnosis of the cause and site of bleeding was made in 65% of patients.

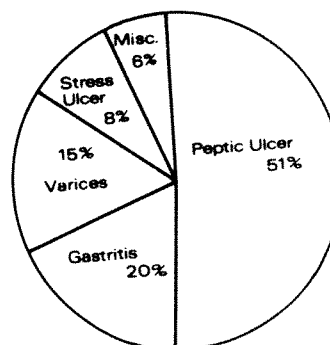


FIG. 7. The primary causes of bleeding in 130 operated patients were predominantly benign peptic ulcer disease and gastritis.

nosed by such studies in 90% of patients subsequently proven to have ulcers. Barium swallow showed esophageal varices in 72% of patients found to have varices on endoscopic examination. Of 44 patients with acute mucosal lesions diagnosed by endoscopy, barium studies were normal in all but one.

Laparotomy

Of the entire 585 patients treated for upper gastrointestinal bleeding, 130 (22%) required laparotomy for 138 episodes of medically uncontrolled hemorrhage (Fig. 3). The proportion of those operated upon fell progressively from 33% in the first year of study to 13% in the fourth year (Fig. 4).

Indications for operations were: 1) transfusion of whole blood exceeding 2500 ml in the first 24 hours; 2) transfusion exceeding 1500 ml in the second 24 hours; or 3) rebleeding after 24 hours of vigorous medical therapy.

Average age of the 130 patients undergoing operation was 51 years (range 15–89 years). Ninety-seven were males and 33 were females.

For 45 patients (35%) who underwent operation we did not have a precise, proven diagnosis of the cause or site of bleeding (Fig. 5). The proportion of such undiagnosed patients was less in year four (15%) when endoscopy and angiography were used commonly, than in year one (43%). When the site of bleeding was unknown at the time of laparotomy, a longitudinal pylorotomy was made for inspection of the duodenum and antrum. If necessary, this was followed by transverse gastrotomy at mid-stomach for inspection of the corpus, fundus, cardia and distal esophagus (Fig. 6). The latter was visualized in some cases by lateral traction on one or more nasogastric tubes passed through the cardia and fixed at the nose.

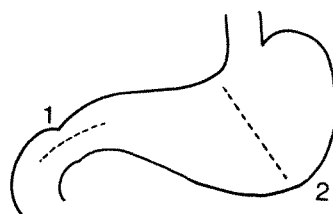


FIG. 6. In patients without a preoperative diagnosis of the cause and site of bleeding, pylorotomy (1) was performed first followed by transverse gastrotomy (2).

Cause of Bleeding in Surgical Patients

The etiology of primary bleeding in 130 surgical patients is summarized in Fig. 7. Benign peptic ulcers accounted for 51% of bleeding lesions (38 duodenal and 28 gastric ulcers). Diffuse gastritis was found in 26 patients (20%), of whom 18 had recently been drinking. Of the eight other patients with gastritis four (50%) had been taking aspirin, phenylbutazone or corticosteroids for one week or longer.

Other causes of bleeding were esophageal varices in 20 patients (15%) and stress ulceration in 10 patients (8%). Eight others (6%) had miscellaneous lesions such as anastomotic (stomal) ulcer (3), Barrett's esophageal ulcer (2), aorto-duodenal fistula (1), gastroduodenal fistula (1) and hemobilia secondary to carcinoma of the gall bladder (1).

Operative Procedures

Three-quarters of the 138 operations performed were selected according to our established protocol which is summarized in Table 1. In the other 25%, the surgical residents, who performed all of the operations under the active operating room guidance of a faculty surgeon, chose to violate the protocol for reasons of the patient's critical condition (25%), technical difficulties (10%) or difference in preference (65%).

Results

Duodenal Ulcer—Poor Risk

Twenty-three of 38 patients operated upon for duodenal ulcer bleeding were judged to be poor surgical

TABLE 1. Recommended Operations for Specific Causes of Acute Upper Gastrointestinal Hemorrhage

Pathology	Operation
Gastritis, Alcoholic	Vagotomy and Pyloroplasty
Gastritis, Non-alcoholic	Vagotomy and Hemigastrectomy
Duodenal Ulcer (Poor Risk)	Vagotomy and Pyloroplasty*
Duodenal Ulcer (Good Risk)	Vagotomy and Hemigastrectomy
Gastric Ulcer (Corpus-Antrum)	Vagotomy and Hemigastrectomy
Gastric Ulcer (Fundus-Cardia)	Vagotomy and Pyloroplasty*
Stress Ulcer	Vagotomy and 75%-95% Gastrectomy
Esophageal Varices	Porto-Systemic Shunt

*Ligate bleeding vessel.

TABLE 2. Results of Primary Operations for Acute Upper Gastrointestinal Hemorrhage

Pathology	Operations	Died	Rebled
Duodenal Ulcer—Poor Risk (23)	V&P (23)	5 (22%)	2 (9%)
Duodenal Ulcer—Good Risk (15)	V&P (4)	0	1 (25%)
	V&Hemigastrectomy (11)	2 (18%)	
Gastric Ulcer—Resectable (22)	V&Hemigastrectomy (22)	3 (14%)	
Gastric Ulcer—Unresectable (6)	V&P (4)	0	
	V&Hemigastrectomy (2)	0	
Gastritis—Alcoholic (18)	V&P (12)	5 (42%)	
	V&Hemigastrectomy (6)	5 (83%)	
Gastritis—Non-alcoholic (8)	V&P (5)	1 (20%)	1 (20%)
	V&Hemigastrectomy (3)	0	
Stress Ulcer (10)	V&P (3)	2 (67%)	
	V&Hemigastrectomy (4)	3 (75%)	
	V&Near-total Gastrectomy (3)	3 (100%)	
Esophageal Varices (20)	Ligation (6)	4 (67%)	2 (33%)
	Portocaval Shunt (5)	0	
	Mesocaval Shunt (7)	2 (29%)	1 (14%)
	Mesocaval (H) Shunt (2)	1 (50%)	

risks (over 65 or another life-threatening disease). All such poor risk patients underwent vagotomy and Heineke-Mikulicz pyloroplasty. In 11 patients the bleeding vessel was oversewn but in 12 others bleeding stopped without direct vessel ligation. Two poor risk duodenal ulcer patients rebled after V&P and five (22%) died within 30 days (Table 2).

Duodenal Ulcer—Good Risk

Of 15 good risk patients bleeding from duodenal ulcer, 11 underwent the recommended operation of vagotomy and hemigastrectomy. Two of the 11 patients (18%) died postoperatively without rebleeding (Table 2). Four protocol variant patients, considered to be good risks, had vagotomy and pyloroplasty. One rebled and required gastric resection.

Of the entire 38 patients with bleeding duodenal ulcer, three (8%) rebled and seven (18%) died within one month of operation. Mortality was 18% following both V&P (27 patients) and vagotomy and hemigastrectomy (11 patients). These statistics lend no support to adding resection to vagotomy as a life-saving procedure for duodenal ulcer hemorrhage.

Gastric Ulcer—Resectable

In 22 of 28 patients with bleeding gastric ulcer, the ulcer crater was in the antrum or corpus of the stomach distal to the cardia. Such lesions were excised by partial gastrectomy. No patient rebled after this operation but three (14%) died in the hospital.

Gastric Ulcer—Unresectable

Six other patients had bleeding ulcers in the proximal

stomach where partial gastrectomy could not be done without trespassing on the esophagogastric junction. The advised operation per protocol in such patients was V&P with biopsy of the ulcer and oversewing of bleeding vessels. This was done in four patients all of whom survived and none of whom rebled. In two similar patients, vagotomy and hemigastrectomy were performed without complication (Table 2).

The overall experience with bleeding gastric ulcers in 28 patients resulted in a mortality rate of 11% and no postoperative rebleeding.

Gastritis—Alcoholic

Eighteen patients had diffuse, superficial mucosal erosions of the gastric corpus and fundus following a prolonged alcoholic debauch. Twelve were treated as per protocol by V&P. None of these continued to bleed but five (42%) died within 30 days (Table 2) of pulmonary disease or sepsis.

Protocol was broken and vagotomy and hemigastrectomy performed in six other alcoholics with gastritis. Although none of these rebled, five (83%) died in the hospital. Survival was thus twice as good when V&P were performed than when the stomach was partially resected for alcoholic gastritis.

Gastritis—Non-alcoholic

Among eight patients with non-alcoholic gastritis, operative treatment was V&P in five, of whom one rebled and later died (20%), and vagotomy and hemigastrectomy in three, none of whom rebled or died (Table 2).

The overall mortality of patients requiring surgery for

gastritis was 42% (11 patients). One death followed rebleeding.

Esophageal Varices

Twenty patients bleeding from esophageal varices did not respond to nonoperative forms of therapy such as esophageal balloon tamponade or infusion of vasopressin into the superior mesenteric artery. Six such patients had transthoracic suture ligation of varices alone. Four (67%) died, two after rebleeding. Two have survived without rebleeding for more than three years (Table 2).

All five patients who underwent emergency end-to-side portocaval shunting survived and none has rebled during a mean followup period of 22 months.

A sixth portocaval shunt was constructed in a patient who rebled after ligation of esophageal varices. This patient did not rebleed but died of liver failure after three weeks.

Seven patients had mesocaval shunting for bleeding varices. In each, the iliac vein was sutured end-to-side to the superior mesenteric vein. One of these patients rebled and two (29%) died postoperatively. The five survivors have not rebled during a mean 20 months of followup.

Interposition H-type mesocaval shunts were constructed in two patients during the last year of study using the Teflon derivative Gore-Tex¹³ as prosthetic vein. Neither patient rebled but one died of hepatic failure 10 days after operation with an open graft.

In the entire group of 20 patients operated upon for bleeding esophageal varices, mortality was 35%. Three patients (15%) continued to bleed after operation and two died.

Stress Ulcer

Ten patients had multiple gastric ulcers after the stress of surgery, trauma, or sepsis. Six of the 10 developed

stress ulceration in relation to sepsis. None had duodenal stress ulcers.

Seven patients had the suggested vagotomy and resection of whom six (86%) died of either respiratory insufficiency or sepsis. None had rebled prior to death. Three of the seven had near-total (85-95%) gastrectomy in an effort to remove all involved mucosa and all died postoperatively. Three stress ulcer patients underwent V&P, of whom two (67%) died.

The hospital mortality of the 10 patients requiring operation for stress bleeding was 80%. No patient rebled. Among other rebleeding patients, however, stress ulcer was encountered twice. Each patient survived after subtotal gastrectomy (1) and oversewing (1).

Rebleeding

Fourteen of 130 surgical patients, (11%), continued to bleed or rebled after operation. Only eight (6%) required reoperation to control persistent or recurrent hemorrhage. The average age of these patients was 56 years. Each received an average 12,000 ml of blood during hospitalization.

Rebleeding was due to disease not previously diagnosed in seven of the eight patients (Table 3). Three patients with duodenal ulcers initially treated by V&P rebled postoperatively and each was found to have hemorrhagic gastritis as the cause of bleeding. Of two patients who continued to bleed after ligation of esophageal varices, one had hemorrhagic gastritis and the other had variceal bleeding. A third patient primarily diagnosed as esophageal varices developed stress ulceration following mesocaval shunt and required subtotal gastrectomy. Stress ulcer was also diagnosed in a patient with primary stomal ulcer bleeding.

Three of the eight patients with rebleeding died although none exsanguinated.

Discussion

Massive bleeding from the upper gastrointestinal tract

TABLE 3. *Rebleeding After Primary Operation for Acute Upper Gastrointestinal Hemorrhage*

Patient	First Diagnosis	First Operation	Second Diagnosis	Second Operation	Outcome
1	Doudenal Ulcer, poor risk	V&P	Gastritis, Non-alcoholic	Subtotal Gastrectomy	Died
2	Duodenal Ulcer, poor risk	V&P	Gastritis, Non-alcoholic	Subtotal Gastrectomy	Lived
3	Duodenal Ulcer, good risk	V&P	Gastritis, Non-alcoholic	Subtotal Gastrectomy	Lived
4	Gastritis, Non-alcoholic	V&P	Gastric Ulcer, Resectable	Subtotal Gastrectomy	Lived
5	Stomal Ulcer	Subtotal Gastrectomy	Stress Ulcer	Oversew	Lived
6	Esophageal Varices	Ligation	Gastritis, Non-alcoholic	Total Gastrectomy	Died
7	Esophageal Varices	Ligation	Esophageal Varices	Portocaval Shunt	Died
8	Esophageal Varices	Mesocaval Shunt	Stress Ulcer	Subtotal Gastrectomy	Lived

TABLE 4. *Summary of Results*

Disease	Satisfactory Control of Bleeding	Satisfactory Survival
Duodenal Ulcer	yes	yes
Gastric Ulcer	yes	yes
Gastritis	yes	no
Esophageal Varices	yes	no
Stress Ulcer	no	no

is a clinical manifestation of several diseases each of which requires different operative and nonoperative therapy. A mass reflex technical response, such as partial gastrectomy, no longer is sufficiently precise to be defensible.

Sophisticated endoscopic and angiographic techniques can now provide accurate diagnosis in the majority of bleeders. As a result, management can be more accurately tailored to the responsible lesion. This review of our experience at the Denver General Hospital covers the period of transition in which these advances were recognized and utilized.

There can be no complacency in the management of a disease where operative mortality is 29% even though our results are comparable to those reported from both municipal⁶ and private³ hospitals. Progress requires identifying which lesions are treated relatively well and which are managed poorly. Simplistically, both our results and those of others could be summarized as in Table 4.

The areas in which present management often fails are alcoholic gastritis, esophageal varices and stress ulcer.

Rationale for choosing an operative procedure once the cause of upper gastrointestinal bleeding is known is based upon the following:

Vagotomy and pyloroplasty control bleeding with acceptable mortality. It is a technically simple and rapid procedure. The only argument is whether, in good risk patients, under ideal conditions, vagotomy and hemigastrectomy should not be performed because of the lower rate of ulcer recurrence following this operation.⁸ Among our patients, mortality was the same (18%) after vagotomy and resection as after vagotomy and pyloroplasty.

Gastric Ulcer

Excision must remain the cornerstone of operative treatment of bleeding gastric ulcers. Partial gastrectomy and vagotomy effectively stop hemorrhage with good survival (86%). Benign ulcers, which cannot be resected without destroying the cardio-esophageal junction, should be treated first by vagotomy and drainage. Our experience in a small number of patients suggests that bleeding can be controlled by such a limited procedure.

The role of vagotomy with resection for gastric ulcer is not established⁹ but we favor reducing gastric acidity as well as excising distal stomach.

Gastritis

The high incidence of gastritis as a cause of massive upper gastrointestinal bleeding is increasingly recognized as endoscopy becomes more popular.^{1,4} Vagotomy and pyloroplasty stop bleeding in most patients with both alcoholic and non-alcoholic gastritis. Resection in the latter is not justified. Mortality among alcoholics with gastritis is high (56%) because of frequently associated sepsis, pulmonary insufficiency or metabolic disease. Avoiding surgery by infusion of vasopressor into the left gastric artery may reduce mortality.

Esophageal Varices

Infusion of vasopressor into the superior mesenteric artery stops variceal bleeding in about 70% of patients.² When infusion fails, porto-systemic shunting is indicated. Transthoracic suture ligation of varices is ineffective in stopping hemorrhage or reducing mortality. The shunt of choice, on the basis of our experience, is end-to-side portocaval anastomosis. Recent use of a prosthesis as an interposition mesocaval shunt has been gratifying in terms of technical ease and shortened operative time. In a much larger group of patients, Drapanas⁷ has confirmed this experience, making the interposition procedure our present choice in the operative treatment of varices.

Stress Ulcer

Mortality after surgery for stress ulcer bleeding is alarming.¹⁴ Results of Kirtley, *et al.*¹⁰ showing 65% survival after V&P have seldom been duplicated by others. Death after stress ulcer bleeding is often due to pre-existing disease. Thus, even near-total gastrectomy, which eliminates potential bleeding mucosa, does not improve survival. Still, vagotomy and high gastric resection seem more reasonable operations than V&P, which are followed by excessive rates of recurrent bleeding.¹¹ Nonoperative management of stress ulceration by intravenous corticosteroids¹² or infusion of vasopressin into the left gastric artery⁵ could be tried before surgery, although ultimate mortality of the disease may not be lessened.

Diagnostic and therapeutic approaches to the upper gastrointestinal bleeder will continue to change in the seventies as endoscopy, angiography, infusion techniques and selective surgery are more widely practiced. Whether mortality will be changed thereby remains to be seen. It is likely that a given technique will benefit

one type of bleeder but not another. Nevertheless, these new abilities make more hopeful the treatment of gastrointestinal hemorrhage in this decade.

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Occult Inguinal Hernia in the Female

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Inguinal hernioplasty was performed in a series of 14 female patients with occult inguinal hernias over a period of five years. During this time 194 herniorrhaphies were performed and thus the incidence of repair for occult hernia was 8%. These patients represent a definite syndrome which has not been sufficiently documented in the surgical literature. The condition is defined and the anatomic pathology documented photographically. The mean age in this series was 20 years with a range of 15-45 years. Thirteen of the 14 cases were followed a mean of 10 months postoperatively. Ten of these were considered excellent results and were symptom-free. The remaining three cases were judged as good results but objective evaluation was less conclusive. There have been no recurrences. The anatomic basis for this syndrome has been documented by others. The absence of an impulse on clinical examination is explained on the basis of size of the hernias and the difference in the anatomy between males and females. Occult inguinal hernia in the female is clinically recognizable on the basis of intermittency, character, and localization of pain and after the exclusion of other pathologic conditions. This syndrome should be entertained in the differential diagnosis of lower abdominal pain in the female. Hernioplasty is safe and effective therapy and returns the patient to normal activity.

THE PROBLEM of inguinal hernia has been a source of obvious interest to surgeons and anatomists and references to the subject are well known in antiquity.⁵ Inguinal herniorrhaphy has become perhaps the most commonly performed operation and is assumed a routine procedure in modern times. Yet recurrence rates remain high and students of the subject continue to emphasize the pathologic anatomy and its relationship to proper repair.

It is with this same general interest that a small but clinically recognizable group of female patients with indirect inguinal hernias has come to attention. These patients present with symptoms typical of symptomatic inguinal hernia but without a definite detectable impulse. The diagnosis is primarily based on history, localization of pain, and an otherwise normal clinical evaluation. Fodor and Webb² recently reported 12 representative examples of this clinical entity but further review of the literature was

unrewarding. Accordingly, it would appear that further exposure and documentation are needed. Our experience represents 14 such hernias which were repaired in 13 patients over a period of five years. Representative cases are presented.

Case Reports

Case 1. A 15-year-old white female was admitted to the hospital with suspected acute appendicitis. She had complaints of pain in the lower abdomen with associated nausea but no vomiting. She related a two- or three-year history of intermittent pain in the right inguinal area which was characteristically associated with sporting and other strenuous activities. At the time of surgical consultation the patient was afebrile. The abdomen was normal with the exception of mild tenderness over the right internal inguinal ring. No impulse could be felt. The diagnosis of inguinal hernia was made. Right inguinal exploration revealed an indirect sac and a two centimeter fascial defect at the internal ring. Repair was carried out and the patient has been asymptomatic for 18 months.

Case 2. A 20-year-old white female presented with a three- to four-month history of left inguinal pain aggravated by activity and straining. Seven to ten days prior to evaluation she experienced the sudden onset of left inguinal pain while moving furniture. History revealed she was hospitalized 4-6 weeks previously and had undergone numerous studies to elicit the etiology of these complaints. At that time she was seen in consultation by a urologist, proctologist and a gynecologist. Physical examination showed only tenderness over the left internal inguinal ring. Left inguinal exploration demonstrated an indirect sac measuring 2 cm in length and 2-2½ cm in diameter at its neck. Repair was carried out. She was relieved of symptoms until two years later when she developed similar signs and symptoms on the right side. Right inguinal herniorrhaphy was done for similar findings noted on the left side. Followup questionnaire was answered as a successful result 42 and 18 months postoperatively.

Case 4. A 45-year-old white female presented with right inguinal pain of two years duration. The pain was intermittent in nature and precipitated by exertion. Recently this increased in severity and prompted the present evaluation. The patient had a documented history of pelvic tuberculosis in the past and had undergone bilateral salpingo-oophorectomy and total abdominal hysterectomy, in addition to a long course of PAS and INH therapy. Examination revealed localized tenderness over the lower pole of a previous right para-median incision and also overlying the right internal ring. Preoperative studies were normal. Exploration of the abdominal wall

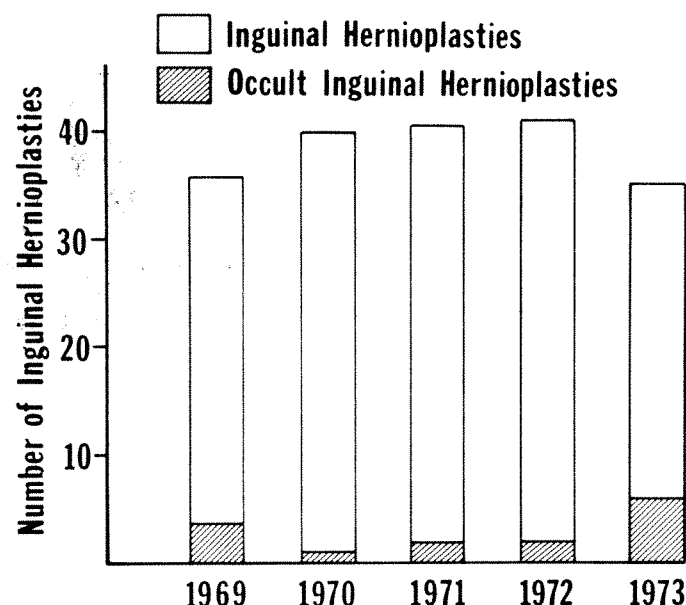


FIG. 1. Incidence of hernioplasty for occult inguinal hernia compared to the total operative experience.

and perhaps laparotomy were indicated. At the time of surgery some nodularity beneath the inguinal ligament and along the inguinal canal was noted. The aponeurosis of the external oblique was divided. A large lipoma of the inguinal canal, an indirect inguinal hernia sac containing adherent omentum, and several hyperplastic lymph nodes were found. The nodes were removed and inguinal herniorrhaphy was carried out. The nodes histologically showed granulomatous lymphadenitis compatible with tuberculosis. The patient was placed on further anti-tuberculosis chemotherapy and has returned to normal as of nine months postoperatively.

Case 5. A 32-year-old white female was referred in surgical consultation because of a two month history of pain over the left internal inguinal ring which radiated down the inguinal canal. The pain was particularly precipitated while lifting her two-year-old son which was a frequent necessity. She further related a history of similar symptoms while performing her duties as a librarian at 25 years of age. There were no other significant symptoms. Examination was normal with the exception of tenderness over the left internal inguinal ring. Barium enema demonstrated an extrinsic defect on the anterior rectum thought to be a retroverted but otherwise normal uterus. At the time of inguinal explora-

tion, an indirect hernia sac measuring 2 cm in length and 2-2½ cm at its neck was found. Repair was performed and the patient was freed of her previous symptoms at the seven month followup.

Discussion

Our clinical experience is fully consistent with that of Fodor and Webb and thus our combined experience represents a total of 26 occult inguinal hernias with one patient having bilateral defects.² The mean age in our group is 20 years with a range of 15-45 years. The hernias occurred with equal frequency on either side. The cases were operated over a five year period during which 194 herniorrhaphies were performed. This represents 8% of the total experience. Figure one emphasizes that operation for the occult hernia is not frequent to the total experience. Indeed, these clinical problems represent a small percentage of patients with inguinal hernia. They, however, most certainly do exist and should be recognized as such. In each case a definite sac was encountered and basically handled with high ligation and repair of the musculoaponeurotic defect at the internal ring; a grade two hernia repair as suggested by Harkins.³ Figure 2 shows the typical operative findings. I prefer to call this syndrome the occult inguinal hernia in the female. This may be defined as a condition of intermittent localized pain directly overlying the internal inguinal ring which may or may not radiate down the inguinal canal, which is categorically precipitated by strenuous physical activity, frequently relieved by rest, and is unassociated with other abnormalities or a definite impulse.

The anatomic explanation of this syndrome has been well documented by others but its clinical manifestations outside of the realm of obvious clinical hernia has not been appreciated. It is generally recognized that a patent processus vaginalis is fundamental in the causation of indirect inguinal hernia in the male.⁸ In the female the analog of this structure is the canal of Nuck which was described by Nuck in 1672.⁴ The structure represents a peritoneal diverticulum

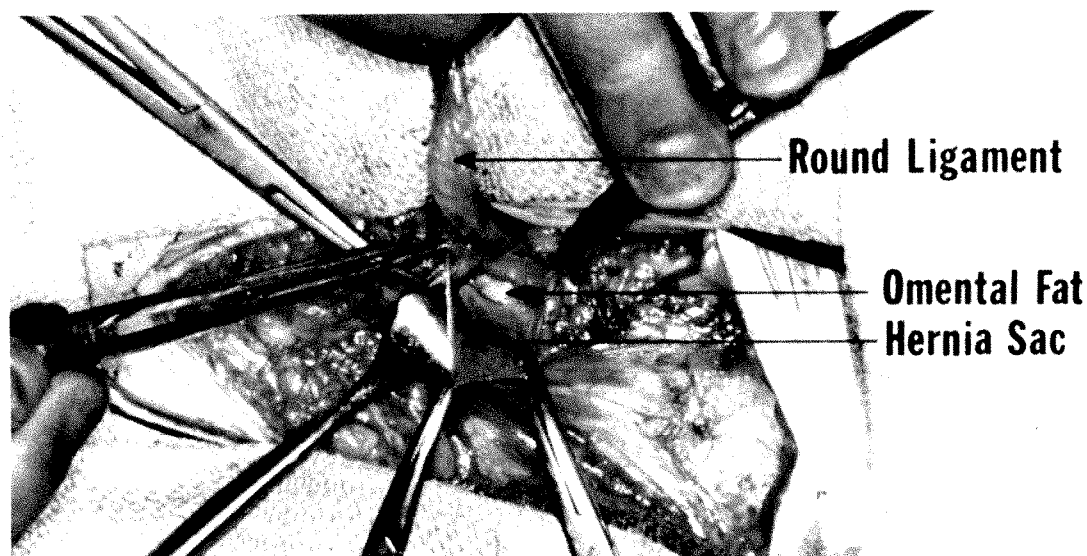


FIG. 2. Case 5. The round ligament is detached from the symphysis pubis and elevated. The hernia sac is dissected and opened. Omental fat is well demonstrated at the neck of the sac.

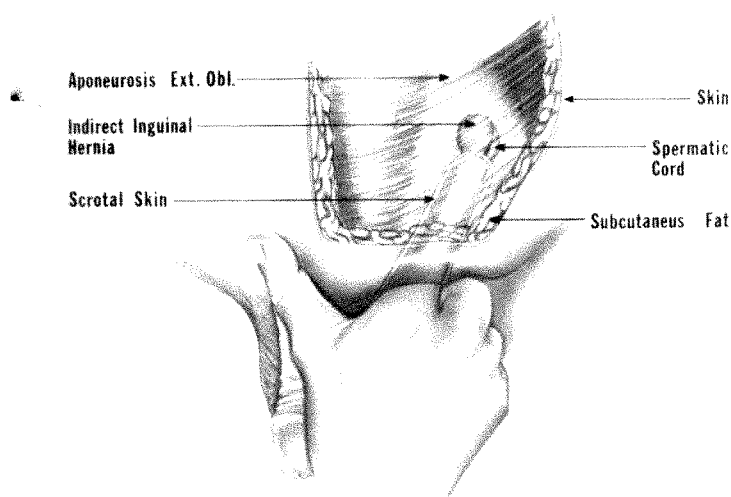


FIG. 3. Clinical examination of the male for inguinal hernia is greatly facilitated by invagination of the scrotal skin and inserting the index finger up in the inguinal canal. The finger is beneath the aponeurosis of the external oblique muscle and can appreciate a hernia impulse through the thin scrotal skin and dartos fascia with considerable accuracy.

in the female much as the processus vaginalis in the male. Investigations by Féré and Sachs indicate patency of the canal of Nuck to be 18% and 25% respectively.^{1,6} Watson quotes another investigator as finding this structure patent in 8–10% of females and a patent processus vaginalis in 30–40% of males. On this basis Watson states, "The presence of empty congenital sacs in adults is more common than is generally supposed. Many people carry these poten-

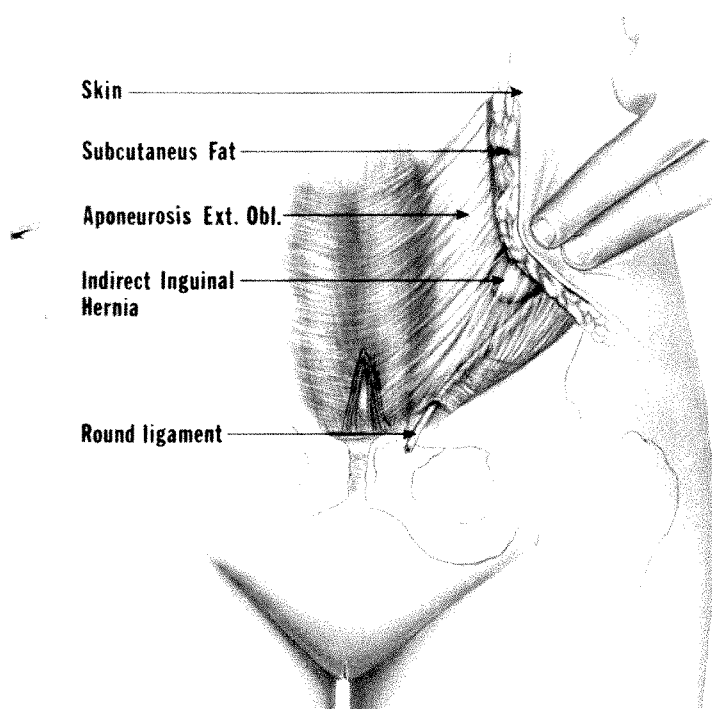


FIG. 4. In the female, the small or occult indirect inguinal hernia is not associated with a palpable impulse since the examining finger fails to appreciate this finding through the barriers of the overlying layers, namely the skin, subcutaneous tissue and aponeurosis of the external oblique muscle. Figures 3 and 4 illustrate this basic sex difference in the diagnosis of certain inguinal hernias.

tial sacs throughout life without evidence of hernia."⁷ Thus it would appear the particular patients under discussion most certainly are those harboring congenital sacs which form the focus of localized inguinal pain in association with sudden exertion resulting in increased intra-abdominal pressure.

The absence of a detectable clinical impulse on examination necessarily requires explanation. The apparent answer is twofold. First, the hernias are, indeed, small and secondly, and perhaps more importantly, there is a sex difference. Our ability to palpate the internal ring in the male is far superior to our ability in the female. In the former we invaginate the scrotal skin, proceed up the inguinal canal, and can appreciate a small indirect impulse. In this setting, the only barriers encountered are the scrotal skin and underlying dartos fascia. This, of course, is impossible in the female and we are forced to detect the impulse via the barriers of the skin, subcutaneous tissue, and finally the firm external oblique aponeurosis (Figs. 3 and 4).

It is suggested that these concepts are of importance in the differential diagnosis of lower abdominal pain in the female. The history of intermittency, character and localization of pain are very typical in occult hernia. Visceral complaints are not common but do occur presumably on the basis of somatic and autonomic neural pathways. Differential considerations are basically gastrointestinal, gynecologic, and urologic. Failure to consider occult inguinal hernia may lead to unnecessary laparotomy.

Finally, it is hoped that further experience with the female occult inguinal hernia will be forthcoming. These patients are young, exceedingly active individuals who are distinctly symptomatic. They very naturally limit their activities and thus have real disability. It is important the diagnosis is made as hernioplasty is safe and curative treatment and restores these patients to normal unlimited activity.

Acknowledgements

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The Value of Laparoscopy in Acute Pelvic Pain

S. O. ANTEBY, J. G. SCHENKER, W. Z. POLISHUK

Laparoscopy was performed in 223 patients with acute pelvic pain but without a definite diagnosis. The clinically suspected diagnosis was confirmed by laparoscopy in only 57 patients (25%). Laparotomy was thus avoided in 145 patients (65%). The endoscopic findings in the three clinical entities included here are presented: tubal pregnancy, acute appendicitis or torsion of adnexal mass.

This study emphasizes the poor correlation between the clinical diagnosis based on history, pelvic examination and physical signs, and the final laparoscopic findings. The value of laparoscopy in evaluation of acute pelvic disease is stressed.

A FREQUENT PROBLEM facing the gynecologist and surgeon is the differential diagnosis of acute pelvic pain.

Too often the physical signs are not specific and the final diagnosis as determined through laparoscopy or during laparotomy differs from that based on clinical grounds.² Laparoscopy, which has been found to be a safe procedure,⁶ aids in establishing the correct diagnosis and treatment.^{4,5}

It is therefore of interest to review our experience with laparoscopy and evaluate its contribution in the diagnosis and management of acute low abdominal and pelvic pain.

Materials and Methods

This study comprises a total of 223 patients in whom laparoscopy was performed to define the diagnosis and management of acute low abdominal pain. These patients were admitted to the emergency room between January 1969 and April 1974.

Laparoscopy was used only in cases where the diagnosis, based on clinical grounds alone, was not conclusive in establishing the management and in order to avoid unnecessary exploratory laparotomy. The indications for laparoscopy according to the suspected clinical diagnosis are presented in Table 1.

Laparoscopy was performed under general anesthesia with an endotracheal tube for controlled ventilation.

After grasping the cervix with volsella, a uterine can-

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nula was introduced into the cervix allowing free mobilization of the uterus. The cannula for inducing pneumoperitoneum was introduced at the lower rim of the umbilicus, after a small semicircular incision of the skin was made. Carbon dioxide was administered through the cannula after appropriate positioning within the peritoneal cavity. The Richard Wolf laparoscope was used.

Results

Cases Suspected of Tubal Pregnancy

In 159 patients suspected of tubal pregnancy, only in 38 (24%), was the diagnosis confirmed (Table 2). Other intra-abdominal conditions mimicking the clinical picture of tubal pregnancy were: ruptured corpus luteum, salpingitis, small ovarian cysts, retrograde bleeding and ovulation bleeding.

Of 28 patients with rupture of corpus luteum, laparotomy was avoided in 19 when no evidence of active bleeding was present. Patients showing signs of peritoneal irritation would have been operated upon if the final diagnosis were based only on clinical grounds and culdoscentesis.

Of 3 cases of hematosalpinx, which mimicked the visual findings of tubal pregnancy with a segmental hyperemic enlargement of the tube, two patients were operated upon. The pathological study of the tubes did not reveal evidence of pregnancy. This experience helped in avoiding laparotomy in a third case with a small tubal swelling.

Cases Suspected of Acute Appendicitis

In 35 patients suffering from acute pelvic pain localized mainly on the right lower quadrant in whom acute appendicitis was considered, the endoscopic examination con-

TABLE 1. *Indications for Laparoscopy According to Their Clinical Diagnosis*

	No. of cases	Confirmed	Operated
Tubal pregnancy	159	38	51
Appendicitis	35	6	15
Torsion of adnexal mass	29	13	12
	223	57	78

firmed appendicular involvement only in 8 cases (Table 3). In two patients salpingitis was also observed.

In 16 patients with a final diagnosis of salpingitis, three were operated upon because there was no possibility of visualizing the appendix through endoscopy.

Surgical intervention was avoided in 20 of the 35 patients suspected of acute appendicitis. There was no pathological finding on endoscopic examination in 6 patients. In two patients where the appendix was not visualized, appendectomy was performed.

Cases Suspected of Torsion of a Pelvic Mass

Twenty-nine patients presented with signs of acute lower pelvic pain, suspected of a pelvic mass (Table 4). Twelve of 29 patients required surgical intervention. The diagnosis of torsion was confirmed in 13 cases. In one case a fibrotic band between the adnexa and abdominal wall causing the torsion was cut and cauterized through the laparoscope.

In 4 cases replacement of an ovarian cyst and puncture of the cyst avoided operative procedure.

Other findings mimicking this clinical entity were subserous pedunculated fibroids, chronic pelvic inflammatory disease, omentum and intestinal masses.

In one patient with signs of pelvic peritonitis associated with an adnexal mass (8 × 8 cm), laparoscopy failed to establish the correct diagnosis, because of omental adhesions. At laparotomy a pyosalpinx was found.

TABLE 2. *Findings in 159 Patients With Suspected Clinical Diagnosis of Tubal Pregnancy*

	No. of Cases	Operated
Tubal pregnancy confirmed	38	38
Rupture corpus luteum	28	9
Salpingitis	23	1*
Small ovarian cysts (follicular or luteal)	28	—
Ovulation bleeding	4	—
Hematosalpinx	3	2
Retrograde bleeding	6	—
Intraperitoneal adhesions	3	—
Normal pelvis†	26	1*
	159	51

*Appendix not visualized.

†Normal intrauterine pregnancy was found in ten patients.

TABLE 3. *Laparoscopic Findings in Patients Suspected of Acute Appendicitis*

	No. of Cases	Operated
Appendicitis	6	6
Salpingitis	16	3
Appendicitis and salpingitis	2	2
Tubo ovarian abscess	5	2
Normal pelvis	6	2*
	35	15

*Appendicitis not excluded on laparoscopy.

The post laparoscopy course in this whole series was uneventful and no complications were encountered among patients with acute pelvic infections.

Comment

Acute low abdominal pain is a common symptom in genital tract disease. No doubt, acute appendicitis, urinary tract infections, regional ileitis or infarcted appendix epiploice¹ may be responsible for this clinical entity.

Patients presenting with acute pelvic pain pose an urgent diagnostic problem and need immediate treatment, and therefore the diagnosis must be assessed during a short period of time. The diagnosis is usually aided by the abnormal physical or laboratory findings. In the clinically obvious cases of appendicitis or ectopic pregnancy, immediate laparotomy is indicated. When physical signs and laboratory tests cannot assist in reaching a definite diagnosis, or when an accurate pelvic examination cannot be achieved, other measures should be undertaken. These include observation, examination under anesthesia, culdocentesis or laparotomy. Except for the last one, all these measures are fallible.

In patients suspected of ectopic pregnancy, laparoscopy was found to be a useful and quicker procedure in establishing a definite diagnosis.¹ Had the diagnosis been

TABLE 4. *Findings in Patients Suspected of Torsion of Pelvic Mass*

	No. of Cases	Operated
Torsion of ovarian cyst	10	6
Ovarian cyst	5*	2
Torsion of adnexa	3†	2
Subserous pedunculated fibroids	2	1‡
Chronic P.I.D. (presented as hydro, pyo or sactosalpinx)	5	1§
Omentum and intestinal mass	1	—
Normal pelvis	3	—
	29	12

*Two cases punctured and evacuated.

†One case caused by peritoneal adhesion, separated through laparoscopy.

‡Necrotic myoma.

§Failure of laparoscopy because of intra-abdominal and omental adhesions.

based on clinical signs and culdocentesis alone, 29 patients having ruptured corpus luteum with no active bleeding, ovulation bleeding or retrograde bleeding would have been subjected to unnecessary laparotomy. As seen in this series, the diagnosis of tubal pregnancy was confirmed only in 24% of patients suspected. Similar results were observed by Liston.³ The differential diagnosis of acute appendicitis and salpingitis in patients presenting with the clinical picture of a pelvic inflammatory condition, where pain is localized mainly in the right lower quadrant, is sometimes quite difficult. Laparoscopy is indicated in those cases where signs of generalized peritonitis are not observed.

The diagnosis of acute appendicitis was confirmed by laparoscopy in only 8 of 35 patients admitted with this diagnosis. Most of the other cases had salpingitis or tubo ovarian abscess. In this group of patients laparotomy was avoided only when a normal appendix was visualized. In patients suffering from acute salpingitis associated with free intra-abdominal pus, the course after laparoscopy was not associated with added risk.

In patients with acute pain, when adnexal swelling or mass was palpated, torsion of ovarian cyst or adnexa cannot always be excluded. In this condition 17 of 29 patients did not have to undergo laparotomy following laparoscopic scrutiny.

The fact that no complications were encountered in this series points to the safety of the procedure.

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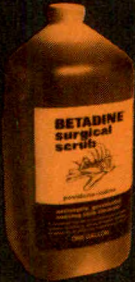
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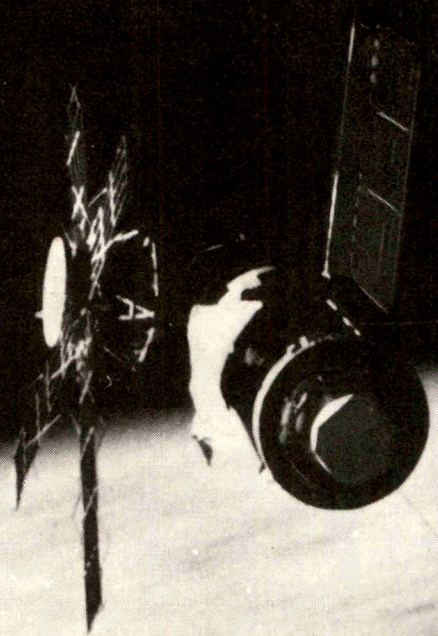
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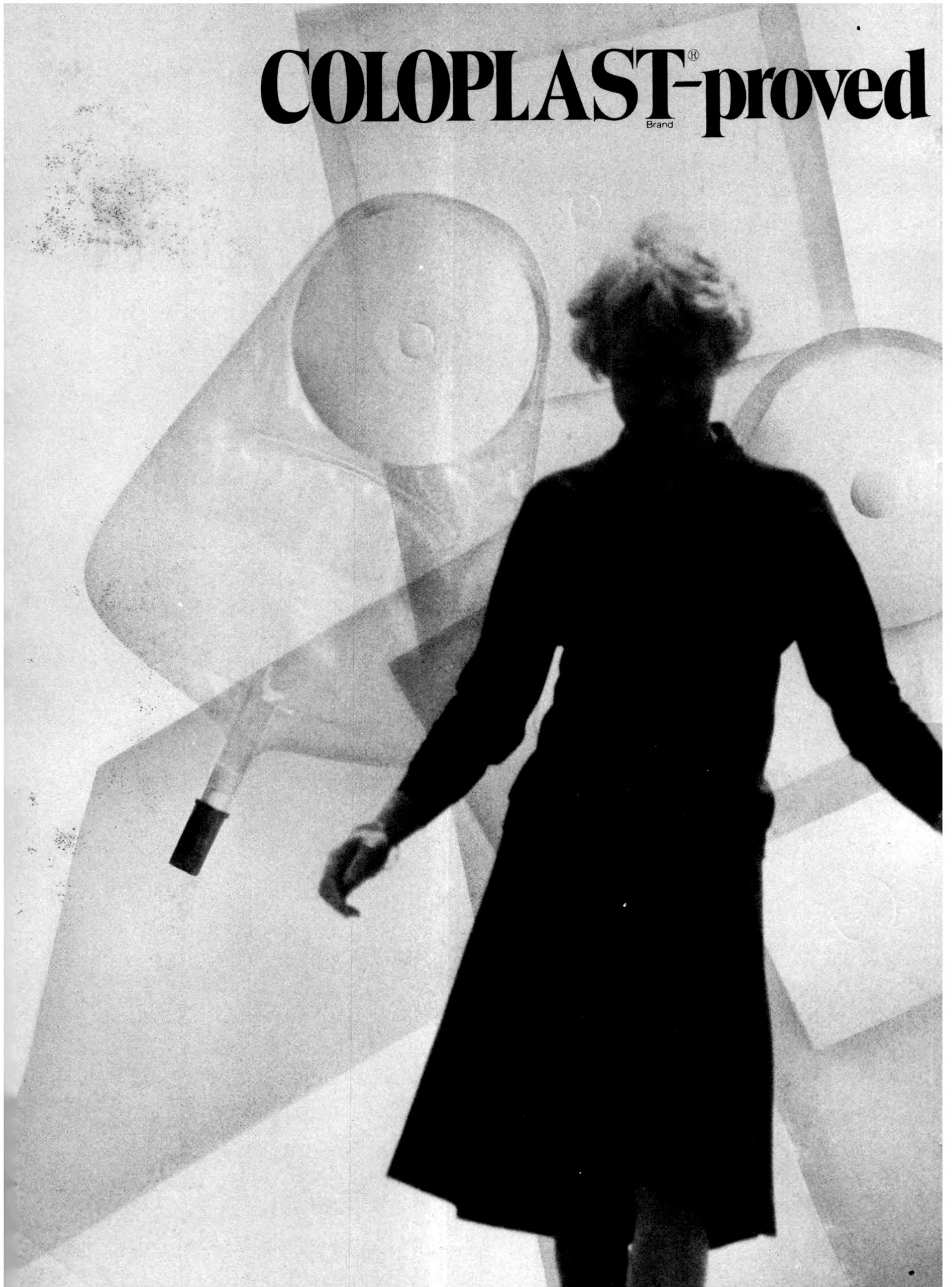
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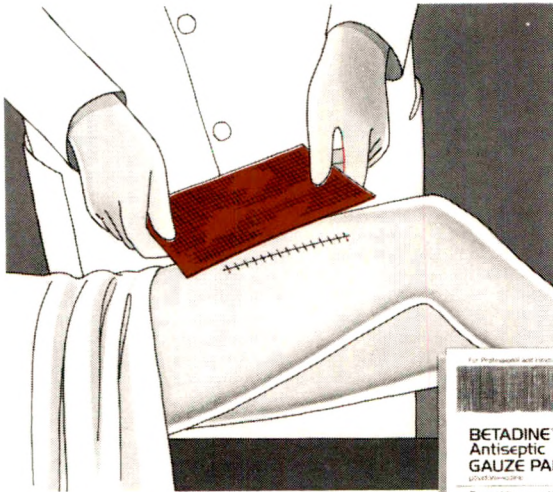
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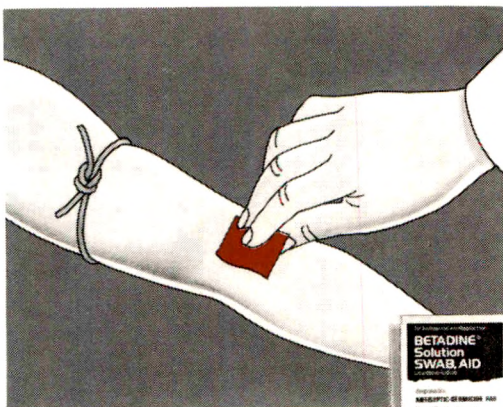
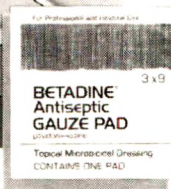
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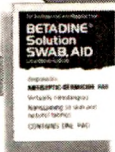
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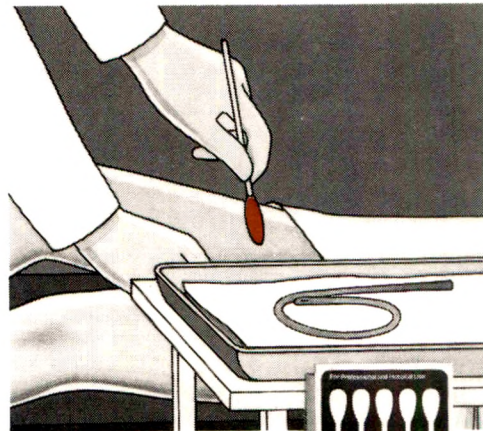


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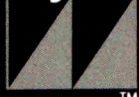
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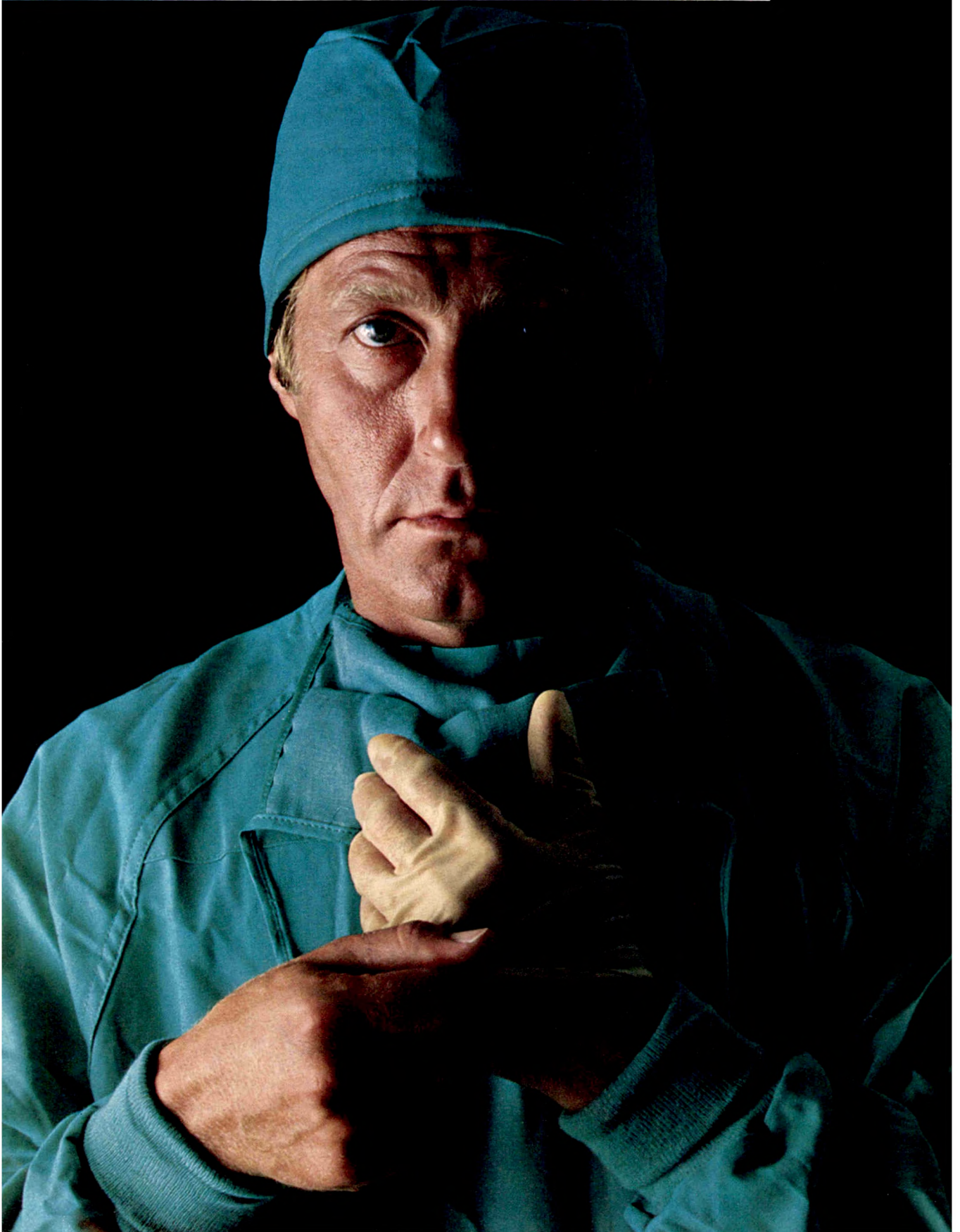
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Tissue/Fluid	Tissue/Fluid Level (mcg/ml) (Sampling time)	Serum Level (mcg/ml) (Sampling time)
Osteomyelitic Bone	49.4 (1 hour)	30.2 (1 hour)
Osteomyelitic Bone	35.6 (5 hours)	26.0 (5 hours)
Osteomyelitic Bone	10.2 (8 hours)	4.8 (8 hours)
Synovial Fluid	50 (1 hour)	85 (1 hour)
	65 (1-1/2 hrs)	78 (1-1/2 hrs)
	59 (2 hours)	53 (2 hours)
	45 (3 hours)	43 (3 hours)
	37 (5 hours)	32 (5 hours)

(Data from individual patients. All patients received 1 gram IM.)

'ANCEF' Offers the Convenience of Both IV and IM Administration

Adverse Reactions

Adverse reactions reported with 'Ancef' include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment. For a complete list of adverse reactions with 'Ancef' therapy, please see next page.

Warning

In penicillin-allergic patients, cephalosporins should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Please see the next page for a brief summary of the prescribing information.

ANCEF[®]
brand of
CEFAZOLIN SODIUM

Injection: 250 mg, 500 mg and 1 gram vials

meets the challenge, IV or IM

ANCEF[®]

brand of

CEFAZOLIN SODIUM

meets the challenge, IV or IM

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

DESCRIPTION

Ancef[®] (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio]-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

<i>Streptococcus pneumoniae</i> (formerly <i>D. pneumoniae</i>)	<i>Klebsiella</i> species
<i>Escherichia coli</i>	<i>Enterobacter aerogenes</i>
<i>Proteus mirabilis</i>	<i>Hemophilus influenzae</i>

Most strains of *Enterobacter cloacae* and indole positive *Proteus* (*P. vulgaris*, *P. morgani*, *P. rettgeri*) are resistant. Methicillin-resistant staphylococci, *Serratia*, *Pseudomonas*, *Mima*, *Herellea* species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis*, *Escherichia coli*, and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'Ancef' is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen,

intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in premature and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest[®] tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocytopenia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible gram+ cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef[®] (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories

Division of SmithKline Corporation, Philadelphia, PA 19101

ANNALS OF SURGERY

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Presidential Address:

Major Contributions to Surgery from the South

DAVID C. SABISTON, JR., M.D.

IN PRESENTING a review of outstanding contributions to surgery from the South, it is intended to emphasize the importance of the past in the development of achievements of the future. In other words, it is not the intent to present a solely historical account, but rather emphasis is placed upon the relationship of these major contributions to the present and future. My personal experiences in the teaching and practice of surgery have led to the firm belief that Santayana captured an enduring truth when he said, "Those who cannot remember the past are condemned to repeat it." It is from our appreciation of earlier contributions that incentive springs for new discoveries and in turn, a continuing stimulus is provided for each new generation of pioneers.

In discussing surgical contributions achieved in the geographic area below the Mason-Dixon Line as shown in an old map of this region (Fig. 1), it should first be emphasized that the Southern Surgical Association is a national organization. Unlike other regional societies, the Southern has a membership drawn from throughout the United States. It is interesting to seek the original basis for a regional organization placing such significance on national membership. In pursuing the subject, one finds that just 3 years after the organization of the Southern, the *Transactions* of the Association contain an opening statement at the 1890 meeting in Atlanta, which is as follows:

Mr. President and gentlemen: I rise on behalf of the Southern Surgical Association to acknowledge that this society, as its name implies, is distinctly Southern but it is far from being exclusively so,

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710

for it has opened wide its doors with a hearty welcome to distinguished men of ability from all sections of our common country. Although only in its third year, its membership has reached the phenomenal growth to a hundred members, among whom are some of the most distinguished to be found in the ranks of surgery throughout the nation.

Although everyone accepts this point of view today and fully understands its importance to the strength of the Southern Surgical, it is nevertheless significant that this philosophy and practice began at such an early date.

In the interest of a more circumscribed subject, these remarks concerning major surgical contributions from the South will be confined to those pioneering achievements by surgeons of the past. To include contemporary contributors would be an undertaking of such proportions as to be beyond the scope of this Address.

It is of considerable significance that, upon the organization of the Southern Surgical in 1887, Ephraim McDowell (Fig. 2) was chosen as its exemplary patron and his likeness appears in gold on the first issue of the *Transactions* of this Association. It becomes clear in pursuing the life and work of this surgical pioneer that he was descended from a courageous and public-spirited family. His father represented Augusta County in Virginia at the Convention of 1775 in Williamsburg. Ephraim was born in 1771 and later moved with his parents to Kentucky and entered the Transylvania Seminary at the age of 15. He studied medicine in Edinburgh where he fell under the strong influence of John Bell, the famed teacher of the day. Returning from Edinburgh in 1795, he

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1974, Boca Raton, Florida.

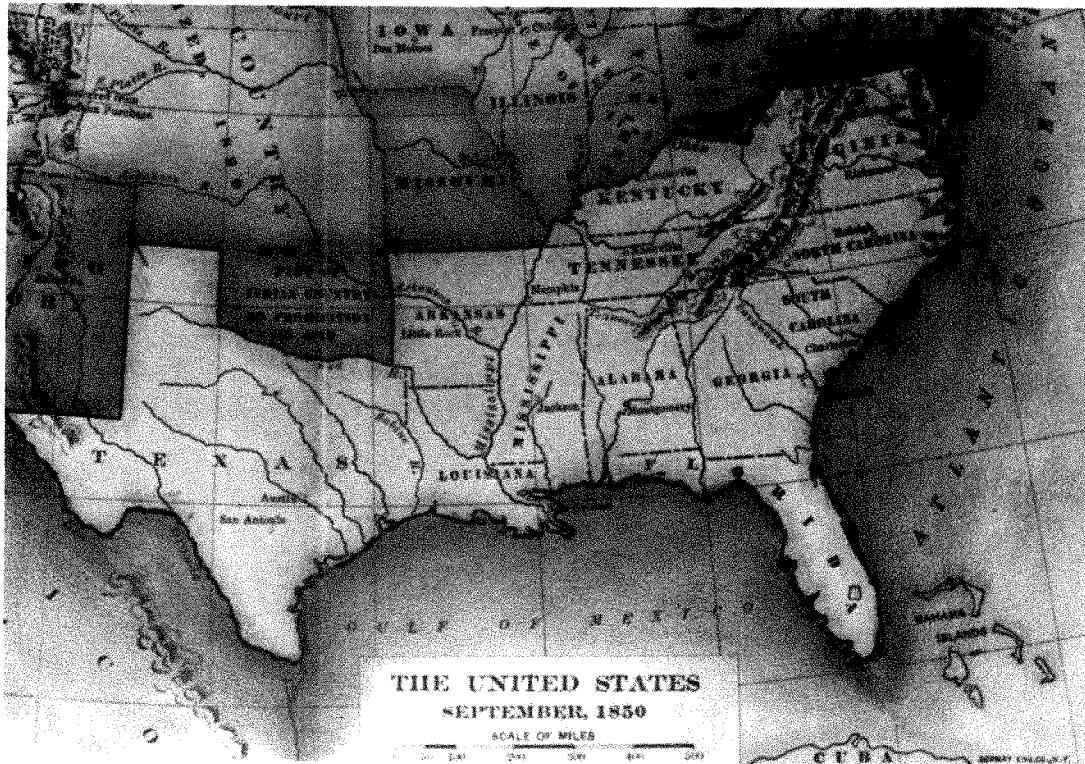


FIG. 1. Old military map showing the Southern States.

entered practice in his hometown of Danville, Kentucky, which at the time was described as "containing upwards of 150 homes and some tolerable good buildings."

The records indicate that McDowell's practice extended over a radius of 50 miles from the town of Dan-

ville, and most of his calls were made on horseback and on many occasions through trackless regions. He was not only a medical practitioner but also a surgeon, being noted in the region for having performed 32 operations for removal of bladder stones (lithotomy) without the loss of a single life. One of his most celebrated lithotomy patients was James Knox Polk, the eleventh President of the United States upon whom McDowell operated in 1812, and who remained a friend for life.

On December 13, 1809, some 14 years after he had entered practice, Dr. McDowell was called to the home of Mrs. Jane Todd Crawford who lived about 60 miles from Danville. Mrs. Crawford had suffered for some time with massive enlargement of the abdomen, first thought to be a pregnancy. But when the mass persisted and the diagnosis could not be confirmed, McDowell stated:

Having never seen so large a substance extracted, nor heard of an attempt, or success attending any operation, such as this required, I gave to the unhappy woman information of her dangerous situation. She appeared willing to undergo an experiment, which I promised to perform if she would come to Danville, . . .²⁰

It is interesting to note the choice of word "experiment" for indeed this was clearly the situation. Until that time there had not been a successful opening of the peritoneal cavity for removal of an intra-abdominal tumor, and this was well known to the thoughtful practitioner in the backwoods of Kentucky.

McDowell's first report of this historic case is to be found in the *Eclectic Repertory and Analytical Review* in 1817 (Fig. 3). It can be seen that he waited until he had managed three such cases before reporting the first. In this paper, he states that Mrs. Crawford undertook the



FIG. 2. Portrait of Ephraim McDowell.

ORIGINAL PAPERS.

Three Cases of Extirpation of diseased Ovaria.

By EPHRAIM McDOWELL, M. D. of Danville, Kentucky.

IN December 1809, I was called to see a Mrs. Crawford, who had for several months thought herself pregnant. She was affected with pains similar to labour pains, from which she could find no relief. So strong was the presumption of her being in the last stage of pregnancy, that two physicians, who were consulted on her case, requested my aid in delivering her. The abdomen was considerably enlarged, and had the appearance of pregnancy, though the inclination of the tumor was to one side, admitting of an easy removal to the other.

FIG. 3. Title page of original publication of Ephraim McDowell reporting three experiences of extirpation of diseased ovaria. (From the Eclectic Repertory and Analytical Review, 7:242, 1817.)

journey from her home in Danville on horseback which required several days. On Christmas Day 1809, McDowell performed the now famous operation in his home (Fig. 4).

The following is McDowell's description of the procedure on Mrs. Crawford: (At this point, the author wishes to express much appreciation for the stepwise illustrations of this historic operation, drawn directly from McDowell's detailed operative note by Leon Schlossberg

especially for this occasion. In these beautiful half-tone illustrations, this distinguished medical artist has made a unique contribution to medical history.)

With the assistance of my nephew and colleague, James McDowell, M.D., I commenced the operation, which was concluded as follows: Having placed her on a table of the ordinary height, on her back, and removed all her dressing which might in any way impede the operation, I made an incision about three inches from the musculus rectus abdominis, on the left side, continuing the same nine inches in length, parallel with the fibres of the above named muscle, extending into the cavity of the abdomen, the parites of which were a good deal contused, which we ascribed to the resting of the tumor on the horn of the saddle during her journey (Fig. 5). The tumor then appeared full in view, but was so large that we could not take it away entire. We put a strong ligature around the Fallopian tube near to the uterus; we then cut open the tumor, which was the ovarium and fimbrious part of the Fallopian tube very much enlarged (Fig. 6). We took out fifteen pounds of a dirty, gelatinous looking substance (Fig. 7). After which we cut through the Fallopian tube, and extracted the sac, which weighed seven pounds and one half (Fig. 8). As soon as the external opening was made, the intestines rushed out upon the table; and so completely was the abdomen filled by the tumor, that they could not be replaced during the operation, which was terminated in about twenty-five minutes. We then turned her upon her left side, so as to permit the blood to escape; after which, we closed the external opening with the interrupted suture, leaving out, at the lower end of the incision, the ligature which surrounded the Fallopian tube (Fig. 9). Between every two stitches we put a strip of adhesive plaster, which, by keeping the parts in contact, hastened the healing of the incision. We then applied the usual dressings, put her to bed, and prescribed a strict observance of the antiphlogistic regimen. In five days I visited her, and much to my astonishment found her engaged in making up her bed. I gave her particular caution for the future; and in twenty-five days, she returned home as she came, in good health, which she continues to enjoy.²⁰

FIG. 4. Home of Ephraim McDowell in Danville, Kentucky. The home is preserved and contains the McDowell Museum.



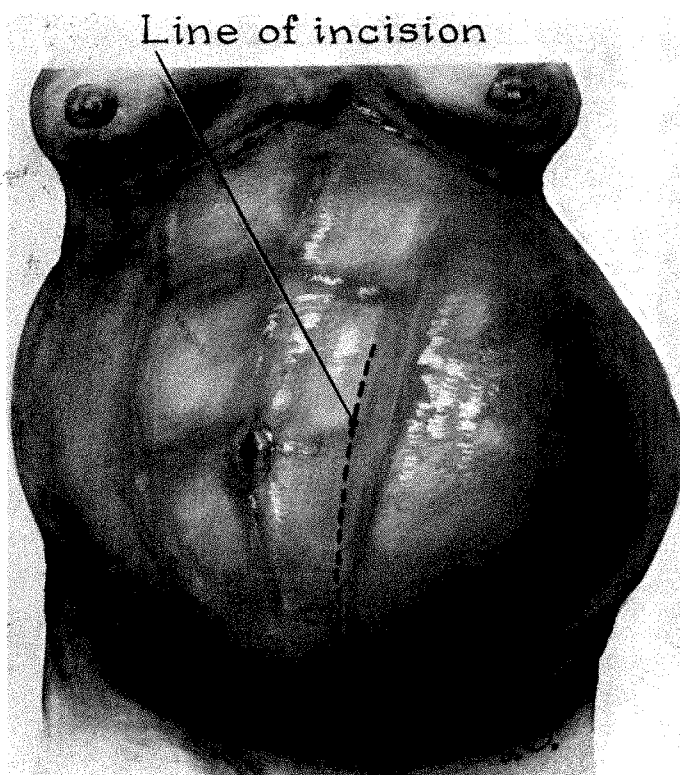


FIG. 5. Incision used to enter abdomen of the first patient operated upon by Ephraim McDowell. (This and the following four illustrations were prepared for this Address by Leon Schlossberg.)

For this operation there was, of course, no anesthetic and Mrs. Crawford's grandson later reported that she read the Psalms throughout the procedure. It is remarkable that this historic achievement, the first successful of its kind in the history of medicine, was ever performed in



FIG. 7. Incision into ovarian cyst with escape of 15 pounds of gelatinous substance.

the first place, was successful, was performed without anesthesia, and was completed in 25 minutes. Mrs. Crawford lived in excellent health with no evidence of return of her disease until her seventy-ninth year (Fig. 10). Her son, Thomas H. Crawford, became a successful businessman and ultimately was chosen as mayor of Louisville.

In 1829, the year before his death, McDowell wrote a letter to a medical student, Robert Thompson, describing a total of 11 patients upon whom he had operated for ovarian tumors with 10 survivors.²⁴ Fortunately,



FIG. 6. Exposure of large ovarian tumor illustrating escape of intestines from the abdominal cavity and ligature of the Fallopian tube.

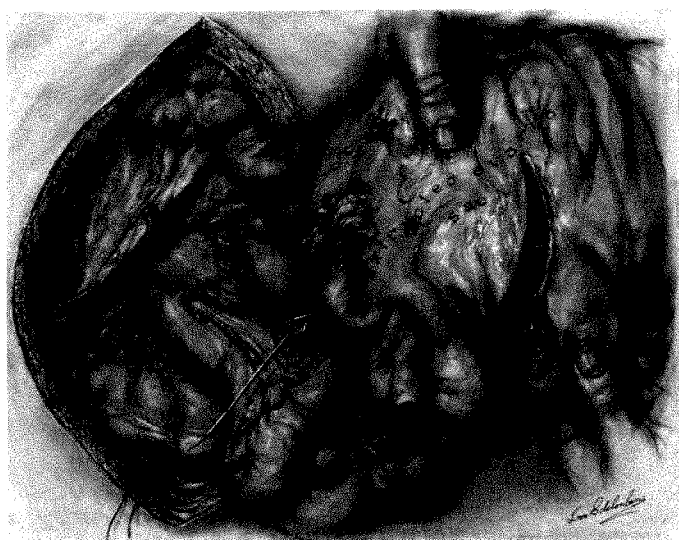


FIG. 8. Extraction of ovarian sac.

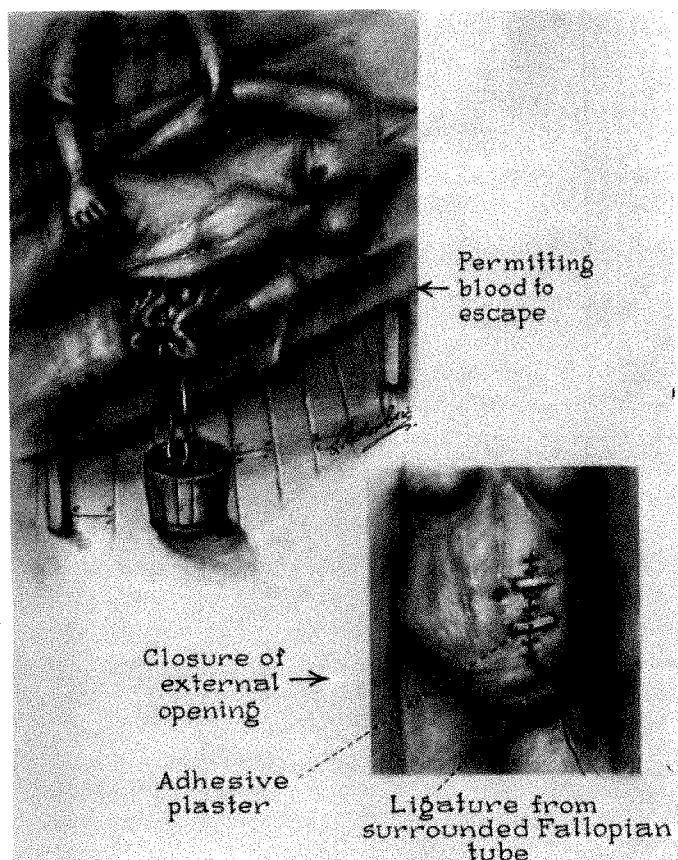


FIG. 9. Illustration of turning of patient to allow blood to escape from peritoneal cavity. Insert: Closure of the abdominal incision.

McDowell received considerable praise for these achievements during his life, and in 1825 he was awarded an Honorary Degree from the University of Maryland. In dedicating the McDowell monument some years later, the noted Samuel D. Gross of Philadelphia stated:

... he achieved that renown which so justly entitles him to be ranked among the benefactors of his race ... an operation which, in its aggregate results in the hands of different surgeons, has already added upwards of forty thousand years to woman's life, and which is destined, as time rolls on, to rescue thousands upon thousands of human beings from premature destruction.⁷

Of all the contributions to surgery, none ranks higher than the introduction of anesthesia, representing as it does a landmark achievement in the progress of medicine. Throughout the history of man, attempts have been made to find appropriate means for alleviation of pain, and while a number of drugs had been successful in part, the challenge remained to find a safe method of producing a state of unconsciousness.

On November 1, 1815, a son was born to the James Long family in Danielsville, Georgia. Young Crawford, as he was named, was a quiet, studious boy who was fond of horses, swimming and fishing. He entered the University of Georgia at the age of 14 and was graduated in 1835. His roommate in college was Alexander H. Stephens, who

was to become governor of Georgia and later Vice President of the Confederacy. Following graduation Long remained for a year in Danielsville, since his father thought he was too young at 19 to enter medical school. He first matriculated at Transylvania University of Lexington, Kentucky, in 1836, but then transferred to the University of Pennsylvania where he graduated in 1839.

In 1799, Sir Humphry Davy had written, "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may be used with advantage during surgical operations, . . ." However, this gas was used primarily by those who wished to demonstrate its more humorous and comical effects and was employed by traveling showmen, one of whom appeared in Jefferson, Georgia, during the winter of 1841. It was in that village that Dr. Crawford W. Long had settled, having only two years previously been graduated from the University of Pennsylvania. Also in this town was a private academy, and a number of the students there attended the session given by the visiting showman. The students were impressed that when under the influence of nitrous oxide they did peculiar things including the most ridiculous of antics. Since they knew and related well to Dr. Long, a young man of only 26, they approached him to



FIG. 10. Mrs. Jane Crawford.

Subsequently on revisiting Athens Dr. Long showed me his folio Journal, or account book, in which stand the following entries:

JAMES VENABLE

March 30, 1842—Ether and excising tumor	\$2.00
May 13, 1842—Sulphuric ether	.25
June 6, 1842—Excising tumor*	2.00

FIG. 11. Data from Dr. Crawford Long's account book of 1842. (From Boland, F. K.: *The First Anesthetic. The Story of Crawford Long.* Athens, University of Georgia Press, 1950.)

obtain some laughing gas. He told them that he had none but mentioned the similar effects of ether. He recalled to them a lecture he attended in Philadelphia, where a showman induced inebriation, not with laughing gas, but with ether. The students returned to school with the news, and this marked the beginning of the now famous ether parties which were held two or three evenings each week in Crawford Long's office. As a matter of fact, the young ladies of the community soon heard of these sessions and finally were successful in persuading Dr. Long to allow them to attend. As might be expected, he was reluctant to let them inhale ether, saying one could not predict what might happen while they were under the influence and he would not want them to do anything which they might later regret. Instead of diminishing their interest, this apparently increased it, and they jointly replied that they didn't care what happened and wouldn't notice it. Moreover, they assured him that it would not be his fault but the fault of the ether should anything untoward occur. One writer said of this event, "Never had such a course of promises been heard under one roof in Georgia and with the utmost of solemnity."

The actual story of the first patient to whom ether was given as a planned anesthetic for a surgical procedure is carefully and authentically described.² One of the students in the local academy in Jefferson, James Venable, consulted Crawford Long about a tumor on the back of his neck, which was causing considerable discomfort. He had attended some of the ether parties, and after a long discussion they agreed that it should be removed using ether as an anesthetic. For historical purposes, it is interesting that the student permitted several of his classmates to see the procedure. Moreover, in order to lend proper respectability to the occasion, the principal of the academy was invited as well. On March 30, 1842, James Venable appeared in the office of Dr. Long together with three of his student friends and the principal of the academy. Venable was described as being rather nervous and lay down on the sofa while Long reached for the ether bottle which had been their companion in so many earlier sprees. He poured ether on a towel as he had done many times before, but on this occasion, it was

under different circumstances for he realized he was making an important experiment. The spectators gathered in a group at the back of the room and watched as the patient inhaled both ether and air intermittently. Long pricked his friend with a pin, and when Venable no longer felt it, he reached for the scalpel and removed the tumor. The entire operation took approximately five minutes and when the towel was removed from his face, Venable awakened in good condition. In fact, he had to be shown the specimen to be convinced that it had been removed.

In Crawford Long's account book for the year 1842, one finds a fascinating entry which was later published in the *Boston Medical and Surgical Journal* (Fig. 11). It is interesting to note the fee of this pioneering country doctor for both the anesthetic and surgical procedure.

Further search into these interesting original reports reveals that appropriate skepticism of anything new was just as true in 1842 as it is today, for there were many who said that the ether anesthetic was not directly responsible for the absence of pain in this historic case. It is clear that Long was an objective observer, since after this criticism he had a patient in whom it was necessary to amputate two fingers. One amputation was performed under anesthesia during which there was no pain. The

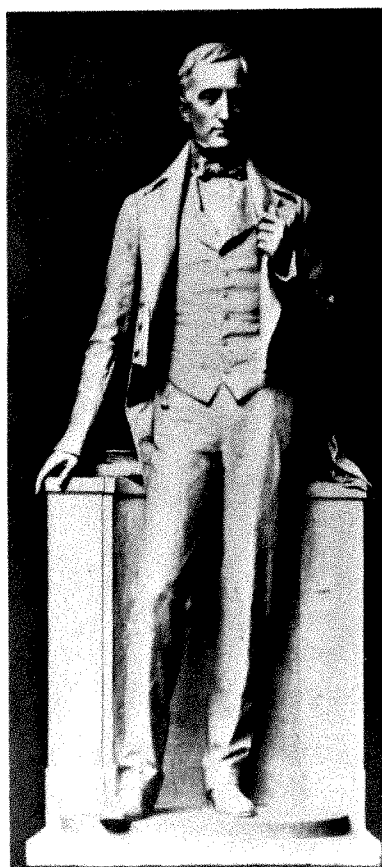


FIG. 12. Statue of Crawford W. Long which stands in Statuary Hall, the U. S. Capitol, Washington, D.C. (From Proceedings in Statuary Hall of the United States Capitol Upon the Unveiling and Presentation of the Statue of Crawford W. Long by the State of Georgia 69th Congress, March 30, 1926.)

other amputation was done in the usual manner of the day, that is, without anesthesia and the young boy cried loudly. To confirm this further, Long removed three tumors from the same patient in one day, the second with ether and the first and third without. Again, the procedure performed with ether was painless as opposed to the excruciating discomfort associated with the removal of the other two lesions.

When the State of Georgia was asked to select its two most distinguished sons to be placed in Statuary Hall of the U. S. Capitol in Washington, Crawford W. Long and another famed historical figure, Alexander H. Stephens, the Vice President of the Confederacy, were chosen (Fig. 12).

In addition to relief of pain, another major impact of this contribution can be best appreciated by citing the fears which surgeons had of the inadvertent movement of the patient during a critical part of an operation prior to the advent of anesthesia. For example, one of America's greatest surgeons, Valentine Mott, said:

... when operating in some deep, dark wound, along the course of some great vein, with thin walls, alternately distended and flaccid with the vital current—how often I have dreaded that some unfortunate struggle of the patient would deviate the knife a little from its normal course, and that I, who fain would be the deliverer, should involuntarily become the executioner, seeing my patient perish in my hands by one of the most appalling forms of death.

In 1912, Long received a medallion from his alma mater, the University of Pennsylvania, with the inscription: "To Crawford W. Long. First to use ether as an anesthetic in surgery, March 30th, 1842, from his Alma Mater."

The proper credit due William T. G. Morton and his associates in Boston is a matter of record, and it is unnecessary to emphasize the importance of their role in broadly disseminating the use of anesthesia throughout the practice of medicine. Nevertheless, the point seems historically clear that the first anesthetic ever to be intentionally administered to man for painless surgery occurred in Jefferson, Georgia, on March 30, 1842. In 1902 when King Edward VII of England awoke from the anesthetic which had been administered during an operation for appendicitis, he asked the surgeon, Sir Frederick Treves, "Who discovered anesthesia?" Sir Frederick answered immediately, "It was an American, your Majesty, Crawford W. Long."²

One of the greatest of the Southern surgeons, J. Marion Sims, has been celebrated worldwide for more than a century (Fig. 13). Born in 1813 in Lancaster County, South Carolina, he received early education in Charleston and later was graduated from the Jefferson Medical College in Philadelphia.

Sims originally began medical practice in his native town of Lancasterville but soon left to settle in Alabama. For a short period he practiced in Mount Meigs and later moved to Montgomery. In the summer of 1845 some



FIG. 13. J. Marion Sims. (From Sims, J. M.: *The Story of My Life* (Edited by his son, H. Marion Sims). New York, D. Appleton and Co., 1886.)

rather unique experiences occurring in swift succession were to greatly influence his professional career. In his autobiography *The Story of My Life*,²⁶ Sims said:

Early in the month of June (1845) Dr. Henry asked me to go out to Mr. Wescott's, only a mile from the town, to see a case of labor which had lasted three days and the child not yet born. He said, 'I am thinking that you had better take your instruments along with you, for you may want to use them.'

Sims found a young woman about 17 years of age who had been in labor for 72 hours with impaction of the head in the pelvis such that labor pains had almost entirely ceased. It was evident that matters could not remain in this condition without the pressure producing a sloughing of the soft parts of the mother, and so forceps were chosen for delivery. She recovered from the immediate effects of the delivery, but due to the prolonged engagement of the head, pressure necrosis and a fistula between the bladder and vagina developed. As Sims said:

Of course, aside from death, this was about the worst accident that could have happened to the poor young girl. I went to see her, and found an enormous slough, spreading from the posterior wall of the vagina, and another thrown off from the anterior wall. The case was hopelessly incurable.

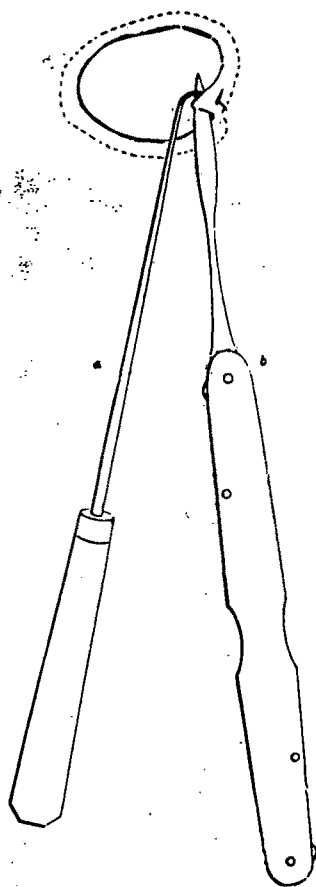


FIG. 14. Demonstration from Sims' original drawing of circumferential excision of the fistulous tract. (From *American J. of Med. Sci.*, 23:69, 1852.)

Sims made a thorough investigation of the literature concerning vesico-vaginal fistulas and continued in his autobiography:

Then, seeing the master of the servant the next day, I said: 'Mr. Wescott, Anarcha has an affection that unfits her for the duties required of a servant. She will not die, but she will never get well, and all you have to do is to take good care of her so long as she lives.' . . . Mr. Wescott was a kind-hearted man, a good master, and, accepting the situation, made up his mind that Anarcha should have an easy time in this world as long as she lived.

Sims considered the condition a medical curiosity since he had been in practice for 10 years and had not seen a single patient with a vesico-vaginal fistula. Strange to say, within a month Dr. Harris from Lowndes County referred Sims another 17-year-old girl, Betsey, who according to Sims, ". . . had a baby about a month ago. Since then she had not been able to hold a single drop of water." As fate would have it, the following month he was referred still a third similar patient, an 18-year-old girl, Lucy, who since childbirth two months previously had been unable to retain urine. Thus, Sims was faced with three young girls who were destined to be social outcasts because of the constant leakage of infected and malodorous urine. He became intrigued with the challenge to help these pitiful young victims and spent the next three years working diligently on each of them,

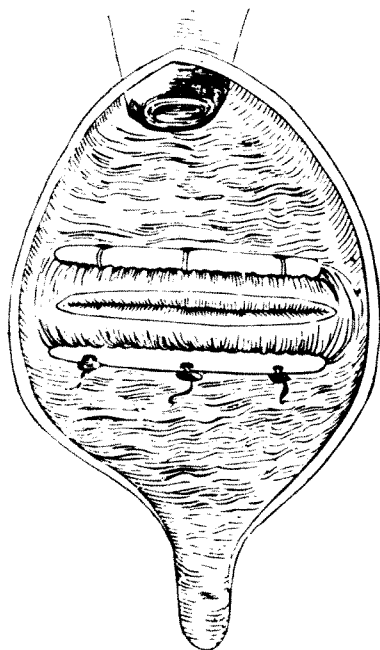
collectively performing more than 40 operations, all of which failed.

Gradually, however, Sims learned from each successive procedure some additional points. He obviously maintained an excellent rapport with his patients, since he states that "one of them alone submitted to more than 20 operations, not only cheerfully but with thanks." Rather poignantly, he summarized these experiences saying, "The history of these three cases is truly interesting in many points, and particularly as exhibiting the slow degrees by which my originally clumsy mechanical apparatus was gradually improved and brought to its present state of simplicity." He finally recognized the significance of several general features of the operation including adequate exposure. In the first procedure he used a silver spoon as a retractor, but to improve this situation he later developed the Sims' retractor, now a classic instrument in surgical practice.

The two surgical principles which Sims ultimately found to be essential for success were: First, after the fistula had been established, epithelium grew from the bladder into the rectum across the granulation site, and he finally seized upon the concept that this tissue must be removed in a circumferential manner such that when approximated there would not be bladder epithelium to rectal suture line. This is shown in his drawing illustrating a hook designed to grasp the ring at the fistulous site to permit excision of the epithelialized area directly by the scalpel (Fig. 14). The second basic surgical principle was the use of special sutures since he had tried all known forms of suture material, but in each instance erosion and infection of the sutures were a serious problem. Finally, he seized upon the idea of using a metallic suture and obtained the aid of a jeweler to make a wire of silver drawn as thin as a horsehair. Then arose the problem of tying such a suture in the limited space and awkward exposure available in the closure of a vesico-vaginal fistula. During the course of a sleepless night, when he was pursuing in his mind for the thousandth time the problem of tying such sutures, he said he suddenly conceived the idea of placing the sutures through a perforated birdshot pellet, pulling the threads tightly, and then compressing the malleable shot to stabilize the suture (Fig. 15).

Sims' dedication, both to his patients and to his dream, is illustrated by the fact that all of these developmental operations were performed in his own small hospital and at his own expense. Thus, in May 1849 he prepared Anarcha for her thirtieth operation. On this occasion the circumference of the fistula was excised and the edges were approximated with four of his fine, flexible new silver wires passing through small strips of lead to prevent cutting into the tissue. The wires were tightly fixed by securing each with a perforated lead shot. A catheter was placed in the bladder, and Sims spent a tedious week awaiting the outcome. On many earlier occasions he had

FIG. 15. Drawing from Sims' original illustration showing use of silver wires placed through metal bars and held in place with perforated lead shot. (From American J. of Med. Sci., 23:69, 1852.)



been certain that when the week came to a close he would witness a successful cure, and he was filled with anxiety and dread. This time, however, the operation was successful. He had shown clearly that the final answer had been achieved by the combination of excision of the circumference of the fistula and the use of silver wires. In rapid succession similar cures were achieved in Lucy and Betsey. Soon the success of his procedure on Anarcha and the others became known throughout Montgomery and surrounding areas.

Despite the medical aid he provided others, Sims himself fell victim to chronic diarrhea and became quite ill. His son contracted the same problem and succumbed from the condition. Sims naturally became alarmed and, thinking a change in climate might be beneficial, spent three months in New York. Upon return to Montgomery, however, he fell ill again. He then sought the curing waters at Cooper's Well in Mississippi, which had gained a reputation for being quite helpful for victims of chronic diarrhea. After trying several other places, he returned North and spent part of the summer in New York and part in Connecticut. Some of his Southern patients followed him to New York for treatment. Dr. Valentine Mott, the noted Professor of Surgery at Columbia, invited him to operate on a patient with a vesico-vaginal fistula, and within a short time Sims' fame had justly spread throughout the North as well as abroad.

Indeed, Sims received a call to attend the most prestigious royal family in Europe. Napoleon III urgently summoned him to his wife Eugenie, the beautiful and sensitive Empress, who had fallen ill. The imperial family was in residence at St. Cloud, and Sims was provided a suite there for his entire stay. He restored the Empress to

health, for which she was deeply grateful. Napoleon III was also extremely kind to Sims and made him a member of the Legion of Honor, a rare honor for a foreigner. Following this royal achievement, Sims experienced a quantum leap. The Emperor Napoleon invited him to serve as Surgeon-in-Chief of the Ambulance Corps in the Franco-Prussian War, and from these experiences he learned much about perforated wounds of the abdomen. His paper, "The Careful Aseptic Invasion of the Peritoneal Cavity Not Only for the Arrest of Hemorrhage, the Suture of Intestinal Wound, and the Cleansing of Peritoneal Cavity But for All Intraperitoneal Conditions," signaled a new era in the field of abdominal surgery. For this reason when President Garfield became the victim of a gunshot wound in 1881, a cable was sent to Sims in Paris for advice. He replied as follows:

If the President has recovered from the shock, and if there is undoubted evidence that the ball has traversed the peritoneal cavity, his only safety is in opening the abdomen, cleaning out the peritoneal cavity, tying bleeding vessels, suturing wounded intestine, and treating the case as we would after ovariotomy, using drainage or not as circumstances require.¹⁴

Although his advice was not followed and the President succumbed, his reply was obviously eloquent as well as succinct. Moreover, these comments are as contemporary today as a century ago.

Fortunately, Sims was honored not only in Europe but in his native country. A statue of Sims stands in New York in Central Park at Fifth Avenue opposite the New York Academy of Medicine, and another stands on the capitol grounds in Columbia, South Carolina. In February 1855, Sims began his drive to found the Woman's Hospital of New York which became a reality, much to his delight. As Wyeth concluded in his Southern Surgical Address in 1895:

It is safe to say that Marion Sims attained the highest position ever achieved in the history of our profession. He stands alone in this; his reputation as a surgeon was so world-wide that in any capital, in any country within the domain of civilization, he could command at any time a lucrative practice. Assuredly, there does not exist in the history of surgery another such distinction. In New York, London, Paris, Brussels, Berlin, Vienna, Rome, Madrid, Lisbon, and St. Petersburg, he found himself everywhere sought after, not only by the patients he could benefit, but by the leading members of his own profession, who were anxious to pay tribute to his wonderful genius.²⁸

Many interesting contributions in the development of vascular surgery originated in the South. In the early experiences, both in this country and abroad, ligation of arteries both for hemorrhage and in the management of aneurysms was fraught with much danger. Ligation of the innominate artery was first attempted by Valentine Mott in New York in 1818, but subsequent infection and ultimate hemorrhage resulted in the death of the patient. The operation was repeated by Hall in Baltimore in 1830 and again by Cooper of San Francisco in 1859, but both attempts ended fatally.

The first successful ligation of the innominate artery

was performed in New Orleans in 1864. In the first issue of the New Orleans Medical Record, Dr. Andrew W. Smyth of the Charity Hospital of Louisiana reported a 32-year-old male with an aneurysm of the right subclavian artery.²⁷ The tumor was the size of an orange, pulsed vigorously, and produced considerable pain as well as numbness in the forearm and hand. For two months the patient had been unable to lie down or to stand erect but was compelled to lean forward continuously for relief of the severe pain and to sleep sitting in a chair with his head resting on the side of the bed. Smyth placed a ligature on the innominate artery a quarter of an inch below its bifurcation and another on the carotid an inch above its origin. On tying the former, the pulsations in the aneurysm ceased. In the postoperative period, a severe hemorrhage from the wound occurred on the fourteenth day producing syncope. With continuing hemorrhage, Smyth elected to place lead shot in the wound in hope that compression produced by the weight of the shot would stop the bleeding. Despite this, the bleeding persisted and on exploration was found to originate from the right vertebral artery which was ligated. The wound healed with subsequent recovery of the patient, and thus another milestone in the history of surgery was achieved. The significance of this contribution is perhaps best described in Samuel Gross's own words when, in a superb monograph entitled "A Century of American Medicine,"¹⁶ he said of this feat:

The case of Dr. Smyth is replete in interest, not only as illustrative of extraordinary ability of the operator, but as showing how recovery may occasionally occur under, apparently, the most desperate circumstances. It is proper to add, that, in all the other cases,

amounting to upwards of a dozen, in which the innominate artery was tied, the result was unfavourable, the immediate cause of death being secondary hemorrhage.

In 1852 a leader was born who was to greatly alter the course of surgery in the United States and the world. William S. Halsted entered Yale where he was not only a scholar but captain of the varsity football team. He attended the College of Physicians and Surgeons at Columbia and chose Bellevue for house training in surgery. Quite early he was struck by the important contributions being made in Europe where he spent the years of 1878, 1879 and 1880 attending the clinics of Billroth, Mikulicz, Von Bergmann, Volkmann, Schede, Esmarch and others. On return to New York he began the practice of surgery and in 1889, at the age of 37, was invited to become Surgeon-in-Chief at the newly opened Johns Hopkins Hospital (Fig. 16). There his attention was immediately drawn to the close relationship of laboratory investigation and clinical surgery, and many of his brilliant operations were performed in the amphitheater before students and surgeons from all parts of the world.

Shortly after his arrival at Hopkins, Dr. Halsted met Miss Caroline Hampton, who soon became his nurse assistant in the operating room. She was descended from the famous Hampton family of South Carolina and was born in the ancestral home of Millwood near Columbia, where she spent her early life. Her father, Frank Hampton, was a Confederate officer and was killed at the Battle of Brandy Station in 1863. Caroline was left in the care of her aunts and uncles including her father's brother, General Wade Hampton who was on General Lee's staff and who later became Governor and United

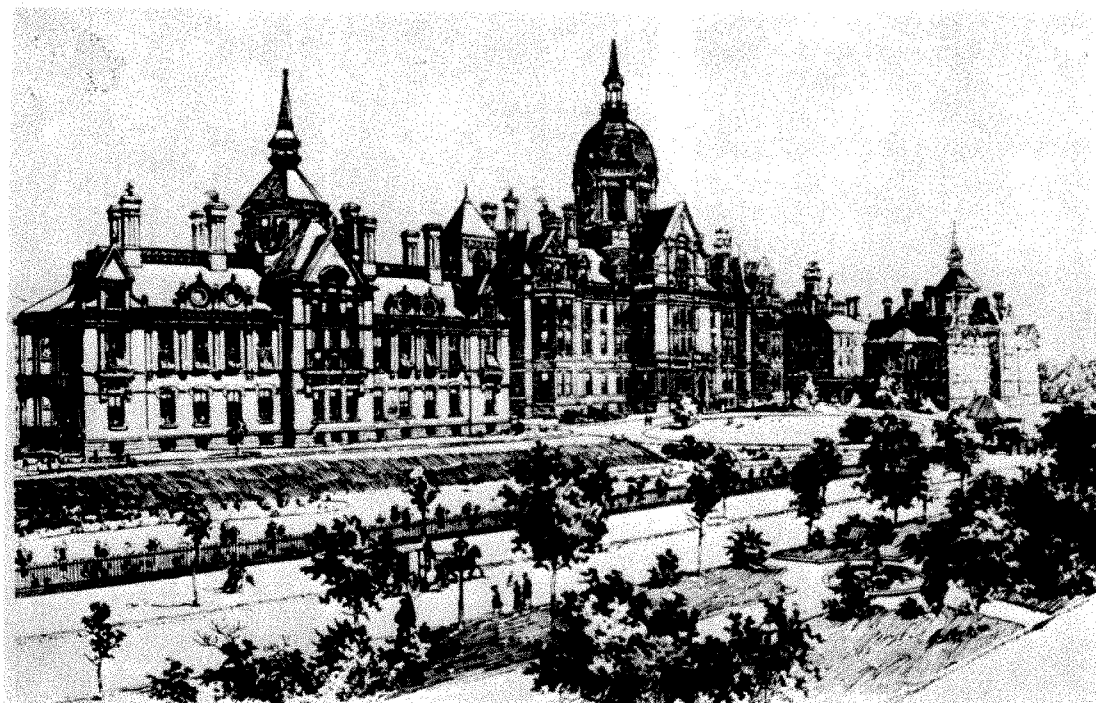


FIG. 16. Etching of Johns Hopkins Hospital at opening in 1889.

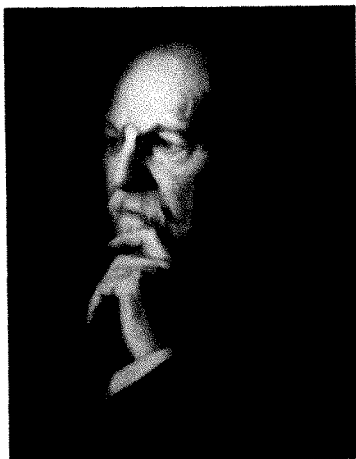


FIG. 17. William S. Halsted.

States Senator from South Carolina. Dr. Halsted became an adopted Southerner both by his move to Baltimore and through his marriage to Caroline Hampton. Moreover, he and Mrs. Halsted spent from May until October each year in Cashiers, in the mountains of western North Carolina, at the original summer estate of the Hampton family. Halsted often commented that the time he spent at their mountain home was the most productive part of his career, since it was there that he wrote and generated new ideas. (Fig. 17).

Mrs. Halsted, who had earlier been the Professor's scrub nurse, was quite prominent in the development of rubber gloves. According to Halsted's own account:

In the winter of 1889 and 1890—I cannot recall the month—the nurse in charge of my operating room complained that the solution of mercuric chloride produced a dermatitis of her arms and hands. As she was an unusually efficient woman, I gave the matter my consideration and one day in New York requested the Goodyear Rubber Company to make as an experiment two pairs of thin, rubber gloves with gauntlets. On trial

these proved to be so satisfactory that additional gloves were ordered. In the autumn, on my return to town, the assistant who passed the instruments and threaded the needles was also provided with rubber gloves to wear at the operations. At first, the operator wore them only when exploratory incisions into joints were made. After a time, the assistants became so accustomed to working in gloves that they also wore them as operators and would remark that they seemed to be less expert with the bare hand than with the gloved hands.¹⁰

It is an interesting fact that Halsted not only introduced the meticulous surgical approach as a fundamental principle of surgery but also used his practical mind to attack the greatest clinical challenges facing surgery in his day. For example, the simple inguinal hernia had resisted a successful operative approach for many years, and in the first report of his unique operation for its correction,⁸ he quoted Shuh who said, "If no other field were offered to the surgeon for his activity than herniotomy, it would be worth while to become a surgeon and devote an entire life to this service." In the current edition of Keen's Textbook of Surgery of that day, it was recommended that operation *not* be performed for hernia if it could be reduced, since the recurrence rate was 27 to 42 per cent within the first year following operation. In his report to the Medical and Chirurgical Faculty of Maryland in 1892, without knowledge of the report by Bassini, Halsted described 58 cases without a single recurrence in those cases which healed per primum in a study covering a three-year period beginning in 1889 (Fig. 18).

Halsted also directed his attention to the management of carcinoma of the breast, which at the time had an amazingly high local recurrence rate. For example, Billroth reported a local recurrence of 82 per cent in the first year following operation, whereas with the Halsted procedure, it was reduced to 6 per cent. When Halsted reported his series of 210 patients in 1907, there was a 1.7

THE RADICAL CURE OF INGUINAL HERNIA IN THE MALE¹

Shuh said, "If no other field were offered to the surgeon for his activity than herniotomy, it would be worth while to become a surgeon and to devote an entire life to this service." Quite as well, certainly, might this be said of operations for the radical cure of hernia. There is, perhaps, no operation which has had so much of vital interest to both physician and surgeon as herniotomy, and there is no operation which, by the profession at large, would be more appreciated than a perfectly safe and sure cure for rupture.

Just now, most of the so-called radical-cure operations are under a cloud. They have not withstood the test of time. Modern textbooks of surgery refer to operations for the radical cure of hernia with more or less misgiving. The newest American surgery² disapproves of operations for the radical cure of reducible hernia if a truss can be worn, and believes that Czerny's method is as good as any, should an operation be necessary.

FIG. 18. Title page from Dr. Halsted's original paper describing his technique for the treatment of inguinal hernia. (From Johns Hopkins Hosp. Bull., 4:17, 1893.)

THE RESULTS OF OPERATIONS FOR THE CURE OF
CANCER OF THE BREAST PERFORMED AT
THE JOHNS HOPKINS HOSPITAL
FROM JUNE, 1889, TO JANU-
ARY, 1894.

By WILLIAM S. HALSTED, M.D.,

OF BALTIMORE,

PROFESSOR OF SURGERY IN JOHNS HOPKINS UNIVERSITY.

FIG. 19. Title page from Halsted's paper reporting original operations for carcinoma of the breast. (From *Annals of Surg.*, 20:497, 1894.)

mortality and a 75 per cent survival when the axillary nodes were negative, and a 25 per cent survival when they were positive. These were remarkable achievements, especially in a day when the vast majority of patients had advanced lesions at the time of first examination (Fig. 19).

In writing about carcinoma of the breast in 1890,⁹ Halsted stated that he began 8 years earlier "not only to clean out the axilla in all cases of cancer of the breast but also to excise in almost every case the pectoralis major muscle or at least a generous portion of it to give the tumor on all sides an exceedingly wide berth."

Halsted also was quite interested in the healing of intestinal anastomoses, since in that day breakdown of such anastomoses was common. In early animal experiments, he demonstrated that in small intestinal anastomoses in which the sutures were taken only through the muscularis but did not penetrate into the submucosa, frequent dehiscence occurred producing suppurative peritonitis and death.¹² However, when sutures included the submucosa, the anastomoses healed perfectly. Dr. Halsted summarized these studies as follows:

1) It is impossible to suture the serosa alone, as advised by authors. 2) It is impossible to suture unfailingly the serosa and muscularis alone unless one is familiar with the resistance offered to the point of the needle by the coats of the intestine. Furthermore, stitches which include nothing but these two coats tear out easily, and are, therefore, not to be trusted. 3) Each stitch should include a bit of the submucosa. A thread of this coat is much stronger than a shred of the entire thickness of the serosa and muscularis. It is not difficult to familiarize oneself with the resistance furnished by the submucosa, and it is quite as easy to include a bit of this coat in each stitch as to suture the serosa and the muscularis alone (Fig. 20).

Halsted was a master of all forms of surgery and in 1899 was the first to successfully remove a carcinoma of the ampulla of Vater. He resected a part of the duodenum, pancreas, and a portion of the common bile duct with successful reanastomosis.¹³ The patient survived but ultimately succumbed to metastases. In 1884, he had shown that nerve trunks could be blocked with cocaine,¹¹ the first clear demonstration of the use of local infiltration anesthesia, and for this the American Dental Association gave him its Medal of Acknowledgment.

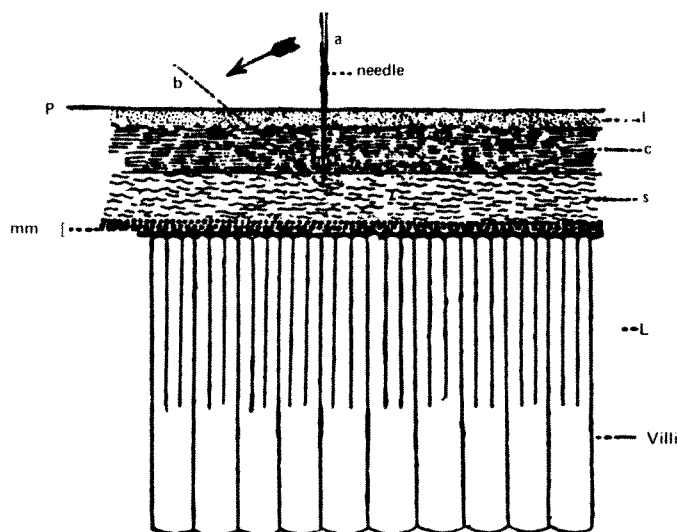


FIG. 20. Diagram from Halsted's work on inclusion of the submucosa in intestinal anastomoses. p. Peritoneum. l. Longitudinal Muscular Coat. c. Circular Muscular Coat. s. Submucosa. mm. Muscularis Mucosae. L. Glands of Lieberkuhn. (From Halsted, W. S.: *Surgical Papers*, "Circular Suture of the Intestine." Vol. I. Baltimore, The Johns Hopkins Press, 1924. pp. 185-211.)

Of all his contributions, many consider the training of surgeons the most significant achievement. Although he was Professor and Head of the Department for 33 years, only 17 Chief Residents completed his program during the entire period. This was due to the long tenure upon which he insisted, particularly in the early days. One is reminded of Mont Reid who, having been in the residency for 11 years, asked Dr. Halsted if he did not think it was time for him to finish the program. Dr. Halsted replied, "Reid, what's the rush?" If one considers the second generation of Halsted residents, one finds an equally impressive number with 37 Professors, 14 Clinical Professors, 18 Associate Professors, and 80 others in academic appointments with 99 in the practice of surgery. In his text on the history of surgery,²¹ Meade summarizes Halsted's career with this statement, "His teachings have had a greater effect on operating techniques in this country than those of any other person."

Few surgeons have achieved the worldwide acclaim accorded Rudolph Matas (Fig. 21). He was born in Bonne-Carre near New Orleans in 1860. At the age of 4 he was taken to Paris, where his father pursued post-graduate work at the Sorbonne. Thus, early in life he was exposed to a scholarly and academic environment and became a man of letters as well as science. Extremely well educated, he spoke English, Spanish, and French fluently and could also read several other languages. He entered Tulane in 1877 and graduated in 1880. In 1882 he became editor of the New Orleans Medical and Surgical Journal, a rare achievement for one of his age, and in

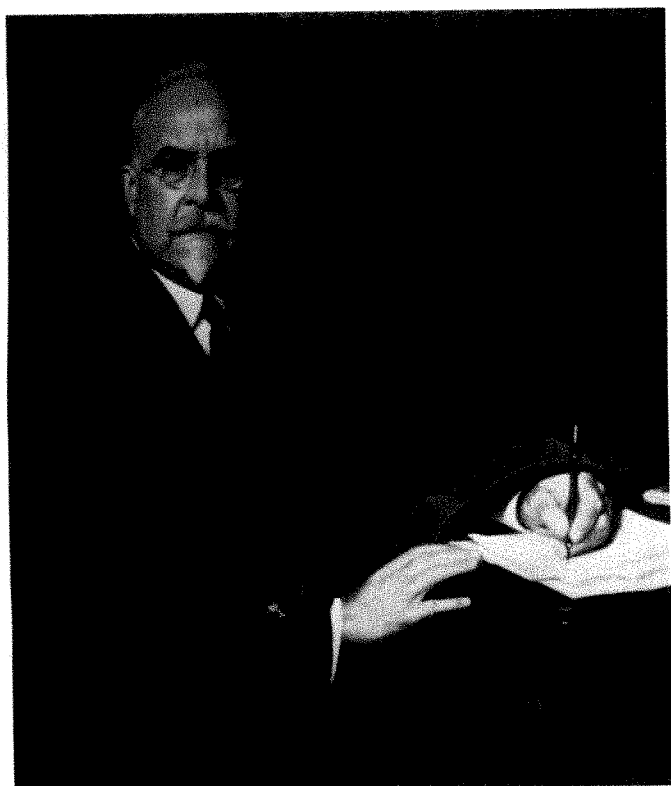


FIG. 21. Portrait of Dr. Rudolph Matas (courtesy of the American College of Surgeons).

1886 was elected President of the New Orleans Medical and Surgical Society. To all of his confreres and visitors from abroad, it was obvious that he was an exceedingly bright and capable young man.

The year 1888 was to become a very important one for Matas, for in that year Manuel Harris, a plantation worker, was admitted to Charity Hospital with a pulsating mass in his left arm, which had steadily increased in size following a hunting accident two months previously. At that time, the standard procedure for the treatment of such an aneurysm was proximal and distal ligation of the main arteries supplying the lesion. This was the procedure chosen, but Matas was quite disappointed some 10 days later to note that the aneurysm continued to pulsate as vigorously as before operation. Therefore, at the end of the second week he reoperated and upon opening the aneurysm, noted three large openings at its base, each bleeding retrograde into the sac. These were then separately closed with sutures with cessation of the bleeding. The procedure was successful, and Matas carefully stored this observation in his mind for future use.¹⁸

More than a decade passed and as the year 1899 drew to a close, Matas was busily engaged in the preparation of a paper for the Southern Surgical on the use of positive pressure apparatus for pulmonary insufflation during surgery. At this time he was asked to see a patient who had suffered a gunshot wound in the thigh while deer

hunting. A large femoral aneurysm had resulted, which was quite painful and was enlarging rapidly. Following standard practice, Dr. Matas ligated the femoral artery both above and below with immediate cessation of the pulsation in the aneurysm. However, the note states that "gangrene occurred immediately after the ligation," and a hasty amputation was required as a lifesaving measure.³ It is of interest that within a month an identical situation developed in another patient and Dr. Matas noted again, "Gangrene of the toes occurred as a sequel to the ligation." These events led him to consider again the possibilities of the procedure he had performed in 1888. The impact of this procedure was emphasized by a third patient, who sustained a gunshot wound to the brachial artery followed by an aneurysm which steadily increased in size and discomfort. Following ligation of the proximal brachial artery in the patient's home, all pulsations immediately arrested and the wound healed per primum. However, within two months the aneurysm returned and was as large as ever. He was fearful of ligating the vessel distally and stated, "I decided to incise the sac and suture the orifices as I had done in the previous case" (of Manuel Harris 12 years before).³ Since the patient would not be operated upon in a hospital, the procedure was done in his home. Two sawhorses were placed with two ironing boards atop them and the patient was strapped securely. The house did not have electricity so it was done by daylight with chloroform anesthesia. An Es-march tourniquet was placed just below the shoulder to occlude the proximal brachial artery, and an incision was then made over the aneurysm and the upper pole exposed. The sac was incised longitudinally and a large mass of mixed clot was evacuated. Two large orifices, one the inlet and the other the outlet of the artery, were now seen in the interior of the sac—orifices large enough to admit the tip of the little finger. These were quickly sealed with

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ORIGINAL MEMOIRS.

AN OPERATION FOR THE RADICAL CURE OF ANEURISM BASED UPON ARTERIORRHAPHY.

BY RUDOLPH MATAS, M.D.,

OF NEW ORLEANS,

Professor of Surgery in the Medical Department of the Tulane University of Louisiana.

FIG. 22. Title page of report of Dr. Matas describing surgical treatment of arterial aneurysms.

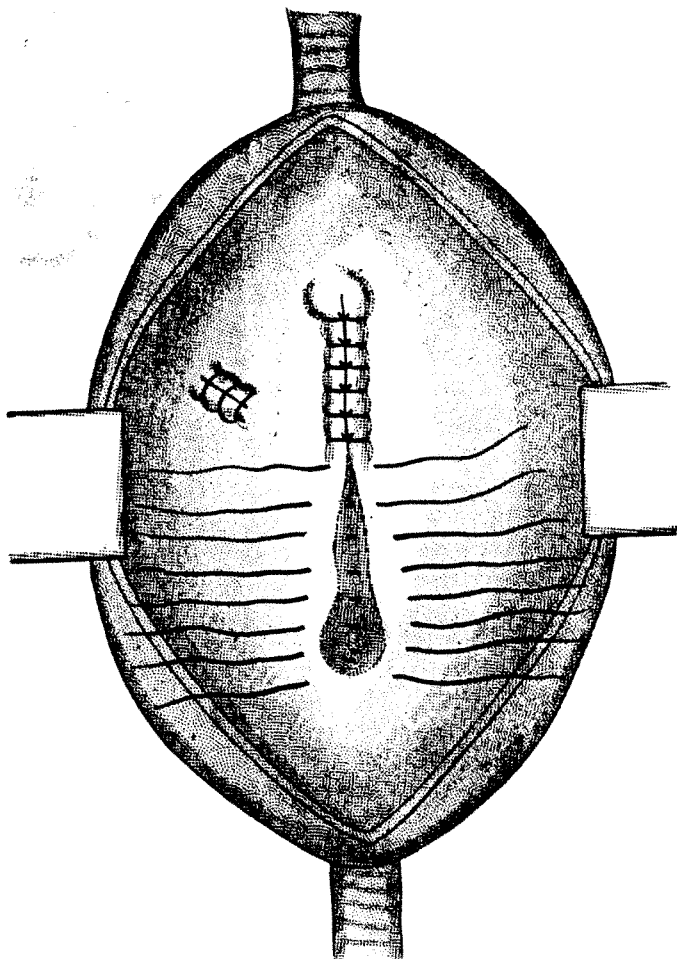


FIG. 23. Illustration of original Matas operation for arterial aneurysms. (From *Annals of Surg.*, 37:161, 1903.)

a fine continuous silk suture which penetrated the entire thickness of the sac wall and these sutures held perfectly. After this, the tourniquet was removed and he was pleased to see that not a drop of blood escaped. In the same year, another patient, a married saloon keeper aged 27, had a similar procedure on a popliteal aneurysm with cure by the newly described Matas endoaneurysmorrhaphy.¹⁹ With these contributions, the modern era of the direct approach to the management of vascular problems was initiated, and Matas formally presented this feat to the American Surgical Association in 1902 (Figs. 22 and 23).

Dr. Matas received many honors in recognition of his contributions, including the presidency of the American Surgical Association, the Southern Surgical Association, and the American College of Surgeons. He was also President of the American Association for Thoracic Surgery and received many foreign honors. It is remarkable to reflect upon the life of a man who was born before the outbreak of the War Between the States and who lived into the atomic age and appeared on television in

1955 at the age of 95. As Howard Mahorner has said of Matas, "He deserved all the adulation and devotion he received from his fellow citizens and from the profession."¹⁷

One of the finest and best known surgeons of this century, the late John M. T. Finney, was a true son of the South. He was born on a plantation near Natchez, Mississippi, in 1863, just three weeks before the Battle of Gettysburg (Fig. 24). His father, the Reverend Ebenezer Dickey Finney, was a Presbyterian minister who also served as principal of a school for boys. Dr. Finney was fortunate in being reared in an exemplary environment with a sound religious background which was obviously to influence him and his notable family for many years to come. He entered Princeton at the age of 17, and upon graduation went to the Harvard Medical School where he achieved an outstanding record and remained for surgical training at the Massachusetts General Hospital.

Shortly after his arrival in Boston, a close associate told him that he was very fortunate in securing a surgical residency there and confided: "From Dr. Porter you will learn how to operate, from Dr. Cabot you will learn how to take care of your patients after operation, and from Dr. Homans you will learn *what not to do*, and I fancy you will probably learn more from him than from either of the others." Later, when his Chief asked him about his

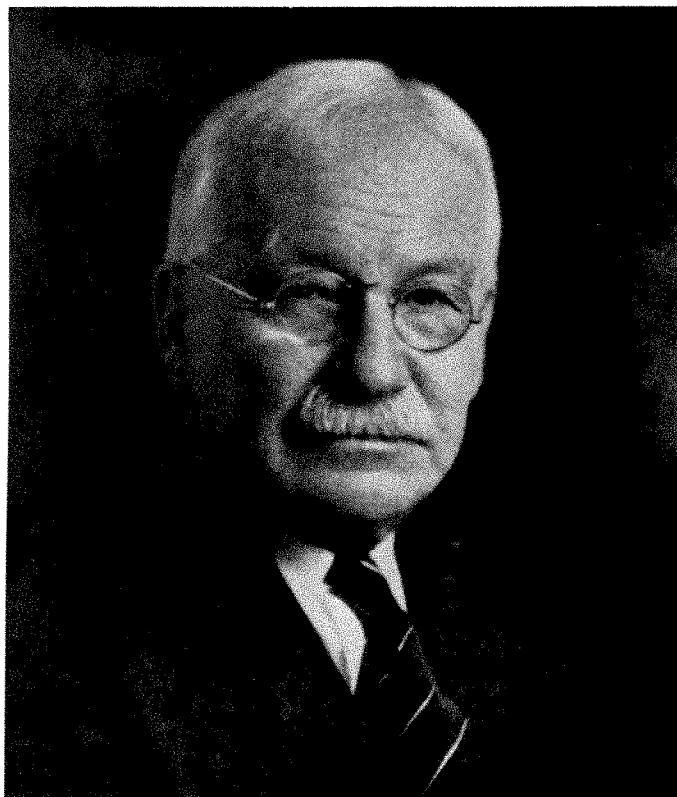


FIG. 24. John M. T. Finney.

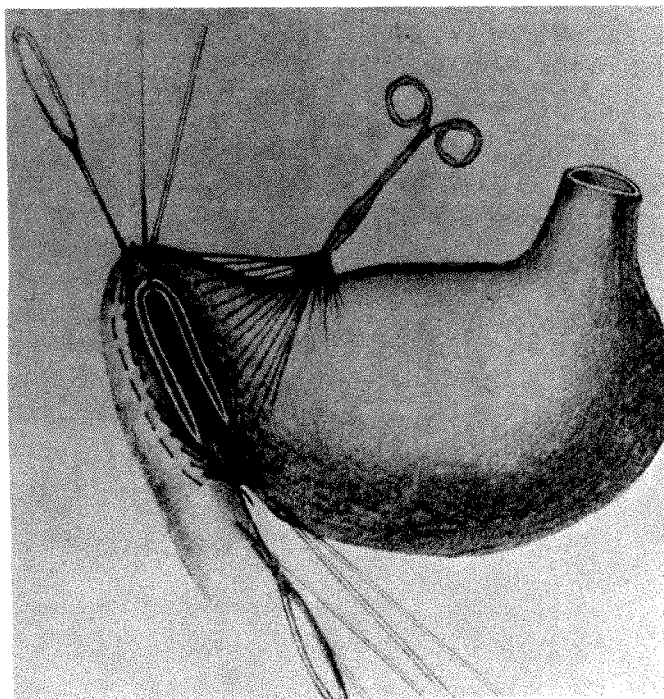


FIG. 25. Illustration of Finney's original pyloroplasty. (From Trans. of the American Surg. Assoc., 20:165, 1902.)

career preference in terms of immediate position, he immediately replied that his first choice would be an appointment with Dr. Halsted at the newly opened Johns Hopkins Hospital.

J. M. T. Finney is particularly well known for his innovative concept of pyloroplasty. In 1902, he performed a gastroduodenostomy without a gastric resection, making a long horeseshoe incision from the lower stomach across the pylorus to the duodenum.⁵ The procedure is shown from the original publication (Fig. 25). The two structures were then sutured together so that a large opening resulted between the stomach and duodenum, which he called a pyloroplasty. He emphasized that the advantage of the procedure over gastroenterostomy was the absence of regurgitation of bile and an unaccelerated evacuation of the stomach. It is interesting to reflect upon his own assessment of the procedure at the time he wrote his autobiography in 1940. He said:

But the contribution which I have made to surgical technique which strikes me as the most outstanding is the plastic operation on the pylorus suggested by me a number of years ago, and known as 'pyloroplasty.' . . . Certain it is that in selected cases, it is very useful in obviating a much more serious and mutilating operation.⁴

Dr. Finney was chosen as the President of the Southern Surgical Association in 1912 and a year later as the first President of the American College of Surgeons. He also received numerous other honors including an offer of the Presidency of Princeton and one from Hopkins to

be Dr. Halsted's successor as Professor of Surgery. Both were declined, the latter primarily because he did not believe in the principle of the full-time system with a fixed, and often inadequate, income. He regarded this of particular significance for those with extensive family commitments.

Clearly, Dr. Finney was one of the most highly respected of all American surgeons, and of his contribution of pyloroplasty, Dr. William J. Mayo was to state before the American Surgical Association that "it constituted the introduction of a new principle in surgery." In retrospect, it is unlikely that either Dr. Finney or Dr. Mayo could have realized at the time the subsequent impact and wide usage that this procedure was to enjoy in the future.

Many contributions to cardiac surgery have their origin in this country, and the first major achievement in this field was made in 1902 by Luther Leonidas Hill, Jr. of Alabama (Fig. 26). The son of a Methodist minister who had moved from Warrenton, North Carolina, some years



FIG. 26. Luther Leonidas Hill.

previously, Luther Hill was born in 1862 and was reared on a farm near Montgomery. He became a distinguished student receiving certificates of distinction in Latin and Greek and later chose to study medicine and was graduated from the New York University. Upon deciding to become a surgeon, he sought further courses at Jefferson Medical College where he studied under Dr. Samuel D. Gross and was awarded a second M.D. in 1882. He then went to King's College in London where he worked under Lister, a teacher who made a very deep impression upon him.

In the 1896 edition of Stephen Paget's "Surgery of the Chest," one finds the following statement:

Surgery of the heart has probably reached the limits set by Nature to all surgery: no new method, and no new discovery, can overcome the natural difficulties that attend a wound of the heart. It is true that 'heart suture' has been vaguely proposed as a possible procedure, and has been done on animals; but I cannot find that it has ever been attempted in practice.

In that same year Ludwig Rehn performed the first successful cardiac suture in Germany. As Pasteur noted many years before, "Chance favors the prepared mind," and so it was that about 1900 Luther Hill began an interest in heart wounds and investigated the subject thoroughly. On September 14, 1902, he was called to the home of Henry Myrick, a 13-year-old boy who had been stabbed five times in the chest. In his report, printed in the Medical Record in 1902, Hill wrote that he was called to see the patient about six hours after a knife blade had been driven into the left fifth intercostal space, about a quarter of an inch to the right of the nipple.¹⁵ The radial pulse was almost imperceptible and the heart sounds were heard with difficulty. The young boy was dyspneic, restless, with cold extremities and had to be aroused to answer questions.

Dr. Hill then proceeded to perform an operation which was the first successful closure of a heart wound in this country. The procedure was described in detail by the author, and again Leon Schlossberg has prepared some superb illustrations of this historic contribution. Dr. Hill's account is as follows:

The wound was about three-eighths of an inch in length, and from it came a stream of blood at every systole. . . . Securing two lamps, I removed the boy from his bed to a table, at one o'clock at night, eight hours after the stabbing, and proceeded to cleanse the field of the operation, and placed the patient in as favorable a condition as my surroundings in the negro cabin would allow. Commencing an incision about five-eighths of an inch from the left border of the sternum, I carried it along the third rib for four inches. (Fig. 27) A second incision was started at the same distance from the sternum and carried along the sixth rib for four inches. A vertical incision along the anterior axillary line was made, connecting them. The third, fourth, and fifth ribs were cut through with the pleura. The musculo-osseous flap was raised, with the cartilages of the ribs acting as the hinges. (Fig. 28) There was no blood in the pleural cavity, but the pericardium was enormously distended. I enlarged the opening in the pericardium to a distance of two and one-half inches, and evacuated about ten ounces of blood. The pulse im-

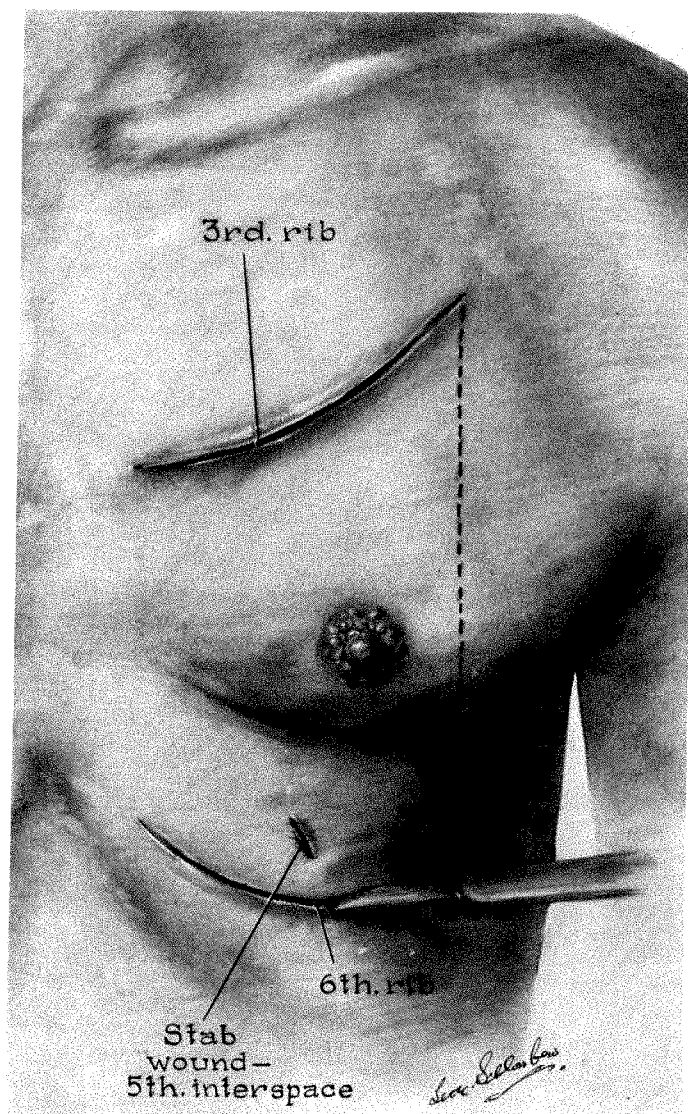


FIG. 27. Illustration of incision used by Dr. Luther L. Hill in first closure of a heart wound to be reported in the United States. (This illustration and the following five were prepared by Leon Schlossberg expressly for this Address.)

mediately improved, and was commented upon by Dr. L. D. Robinson, who so successfully and skillfully administered the chloroform. I had my brother, Dr. R. S. Hill, to pass his hand into the pericardial sac and bring the heart upward, and, at the same time, steady it sufficiently for me to pass a catgut suture through the center of the wound in the heart and control the hemorrhage (Fig. 29). I cleansed the pericardial sac with a saline solution, and closed the opening in it with seven interrupted catgut sutures (Fig. 30). The pleural cavity was also cleansed with a saline solution. (Fig. 31) and drained with iodoform gauze (Fig. 32). . . . On September 17 he commenced to improve, and his recovery has been uninterrupted.

Shortly after this remarkable feat, Professor Sherman wrote, "The road to the heart is only 2 or 3 centimeters in a direct line, but it has taken surgery nearly 2,400 years to travel it."

One cannot mention the name of Hill in the United

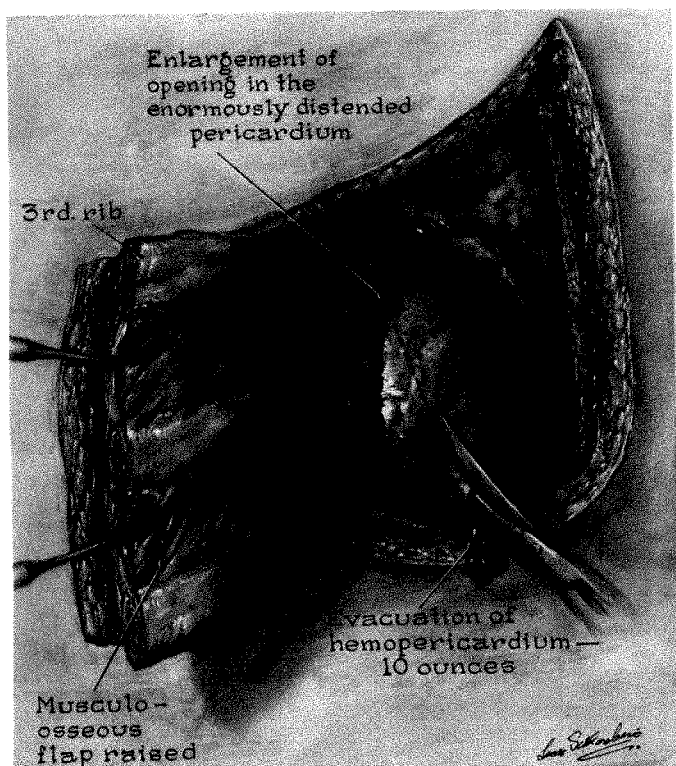


FIG. 28. Opening of musculo-osseous flap to expose hemopericardium with drainage of 10 ounces of blood.

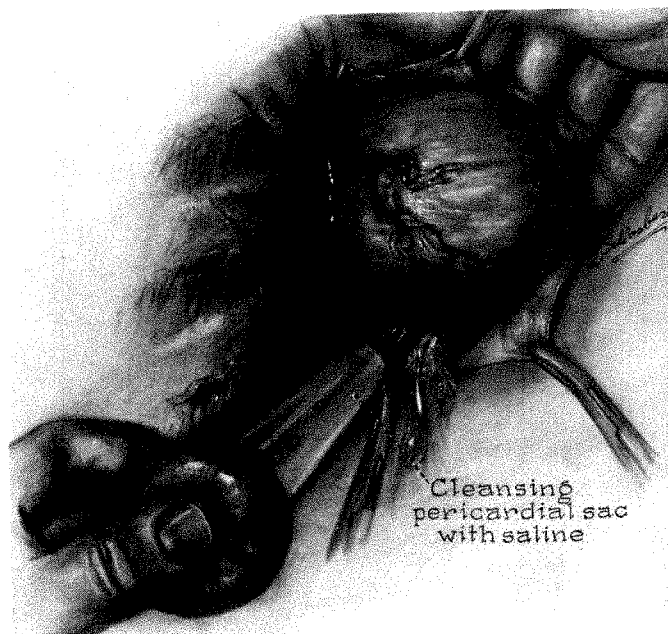


FIG. 30. Irrigation of pericardial cavity with saline to remove blood and blood clots.

States without recognizing its more recent pertinence in the field of medicine. Dr. Luther L. Hill's son, Lister, named for Joseph Lister, was first sent to the United States Congress from Alabama at the young age of 28 and was later elected to the United States Senate in 1938 (Fig. 33). He was the original author of the Hill-Burton Act for

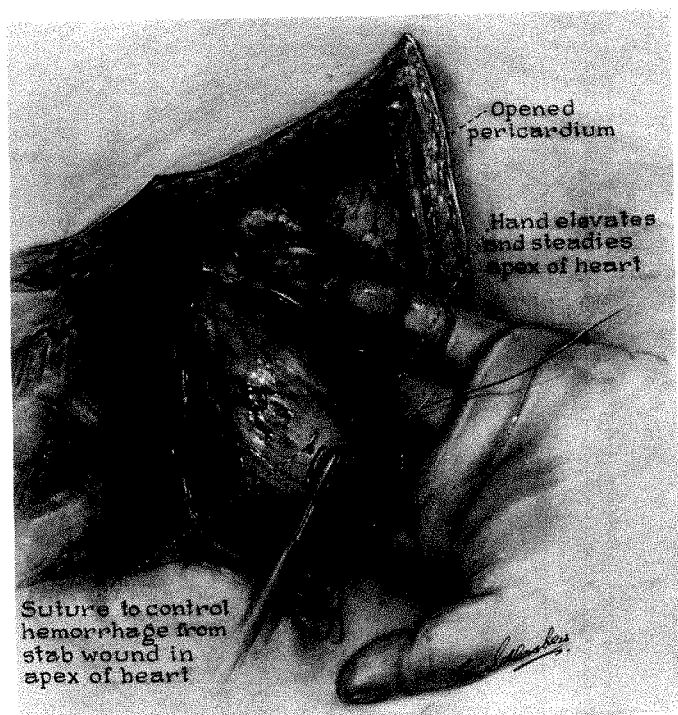


FIG. 29. Placement of suture in apex of heart to control bleeding stab wound.

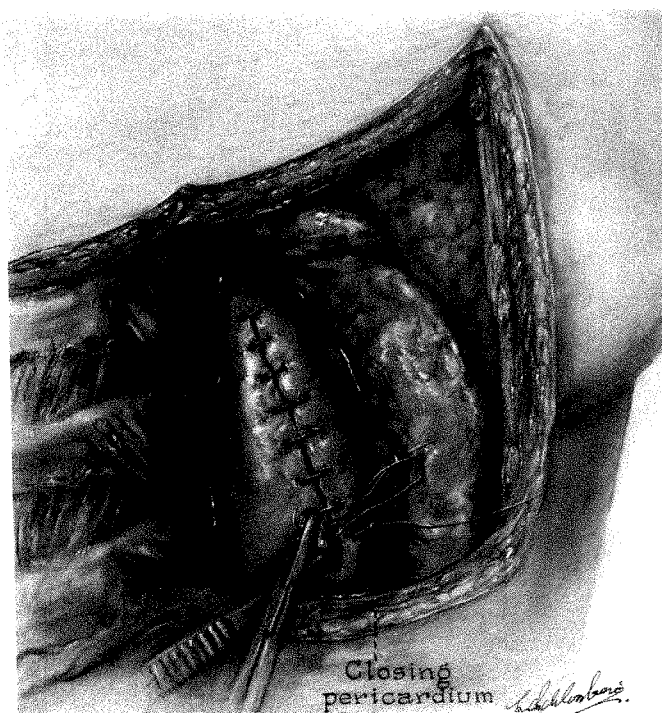


FIG. 31. Closure of pericardium.

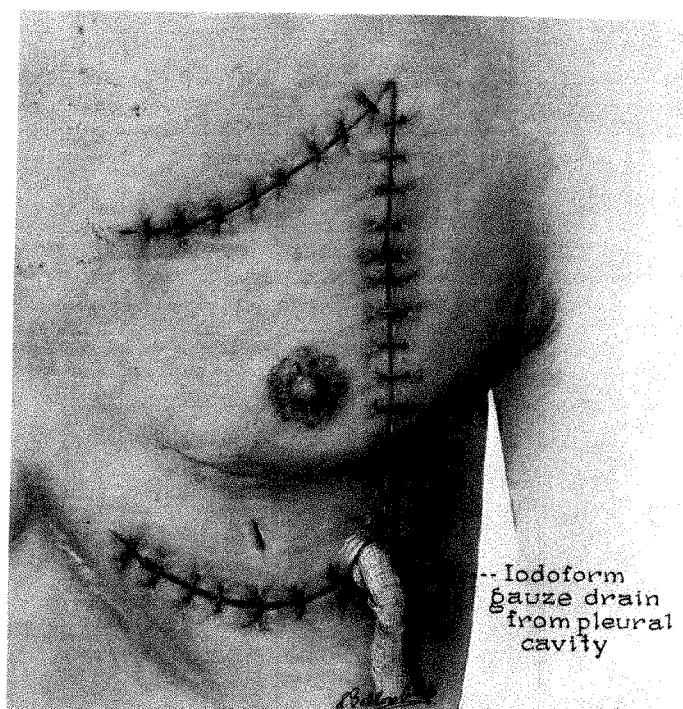


FIG. 32. Closure with drainage.

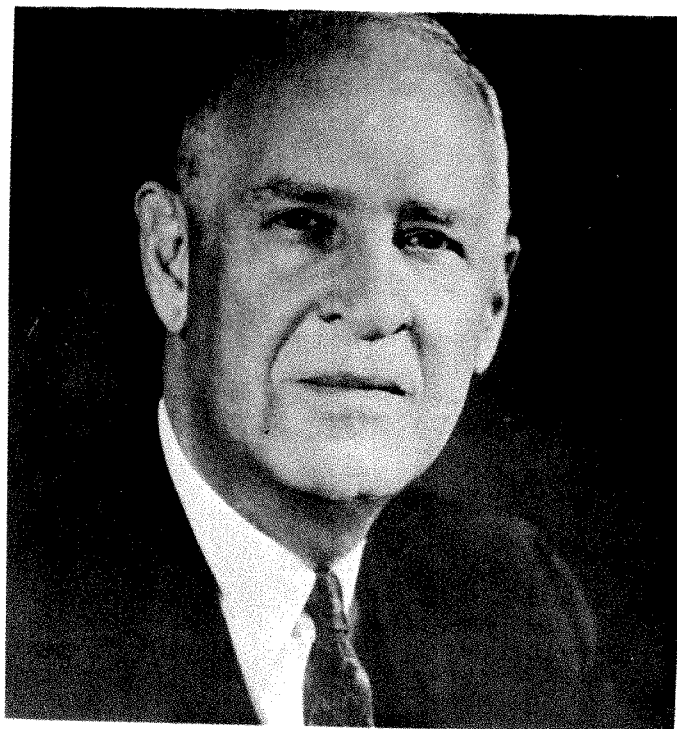


FIG. 33. Senator Lister Hill of Alabama.

the building of hospitals, which, together with his strong support of medical research through the National Institutes of Health, has brought the United States to first place among the nations of the world in medicine. Lister Hill served in Congress for 45 years and was consistently a champion of medical education, research, and patient care. Helen Keller said of him, "My heart grows warm every time I think of you, and that is ever so often."

James A. Shannon, the noted director of the NIH for many years said, "I know that I can express the admiration, respect, and gratitude of the research community for what he has done for medical research in our time."²⁵ In March of 1968, an appreciation dinner was held for him in Washington, D.C., and it was my privilege to have been in attendance. At the dinner, Russell A. Nelson said of him, "Let no one doubt for even a moment that this great man has done more for the building of hospitals in this country than any other person in his generation."²² At that time the President wrote, "If any one man could be called the father of our nation's health, it would be Lister Hill."

The final contributor to be discussed had strong affection, respect, and loyalty for this organization and its members. His original contributions to surgery have been recognized throughout the world, and he did much to advance the total image of the surgeon in this country and abroad. Alfred Blalock was educated at the University of Georgia and at Hopkins and later completed a surgical residency under Dr. Barney Brooks at Vanderbilt (Fig. 34). Remaining on the faculty in Nashville, he was able to

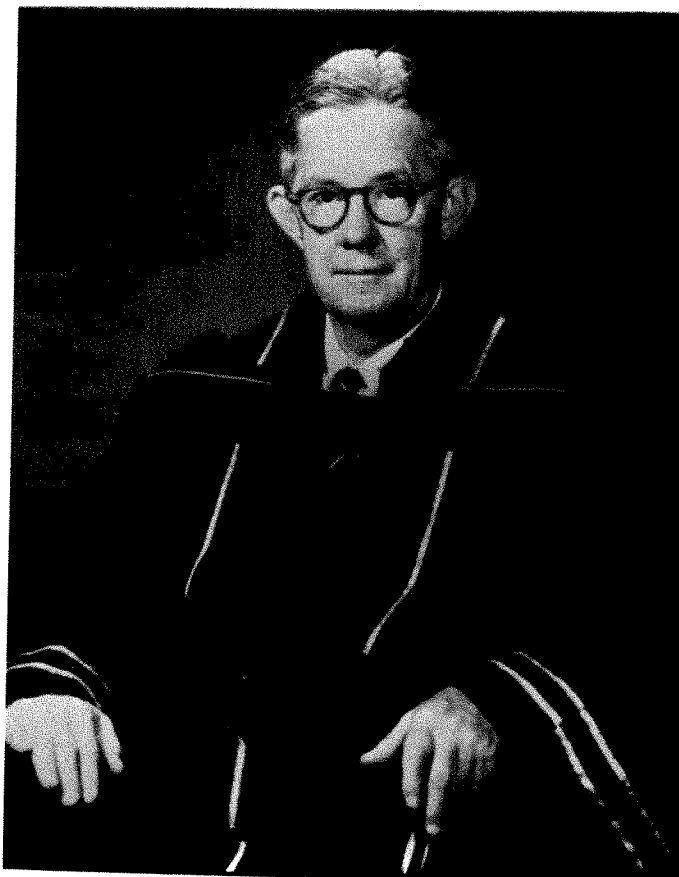


FIG. 34. Portrait of Dr. Alfred Blalock (courtesy of the American College of Surgeons).

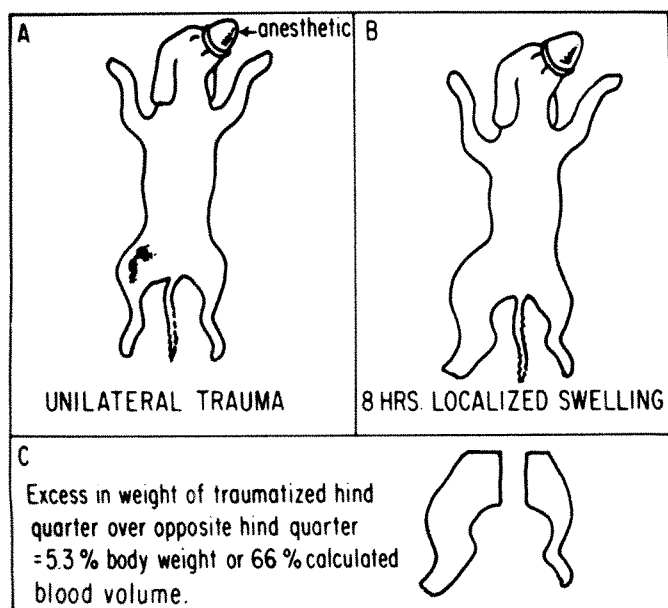


FIG. 35. Diagrammatic illustrations of experimental preparation used by Dr. Blalock to determine the pathogenesis of shock.

devote large segments of his time to basic investigation and quite early began his fundamental work on the pathogenesis of shock. At that time, the status of this important subject was in a total state of disarray with many conflicting views concerning its genesis. The basic experiment which Dr. Blalock designed was performed on the hind limb of an anesthetized animal. The thigh was injured by blunt trauma and eight hours later its weight was compared with that of the control limb after separate dissection (Fig. 35). The increased weight of the traumatized limb was shown to account for 66 per cent of the circulating blood volume and thus fully explained the state of shock. In this simple, yet clearly brilliant experimental study, Dr. Blalock showed that shock is due chiefly to the loss of circulating blood and plasma from the vascular compartment, either externally or into the tissues.

From his monograph "Principles of Surgical Care. Shock and Other Problems," Dr. Blalock summarized his work saying, "Shock was once a surgical complication to be dreaded, but now in the light of recent intensive investigations of its causes it would seem to be largely preventable."¹ For these unique contributions, no less an authority and able critic than Sir James Pickering, the Regius Professor of Medicine at Oxford, said, "The conclusion that emerged from World War I was that shock was a traumatic toxemia produced by the effects of vasoactive substances like histamine released from injured muscles. It needed the genius of your Alfred Blalock and the experience of the Second World War to show that this was not so."

Few investigators make more than one major contribu-

tion, but Dr. Blalock continued his research and proceeded to become a prime leader in the development of cardiac surgery with his brilliant operation for tetralogy of Fallot. It is important to emphasize that this major achievement came directly from his basic observations in the experimental laboratory and, in fact, as a result of experiments on an unrelated subject. In the late 1930s he became quite interested in pulmonary hypertension and attempted to produce this condition in an experimental model by creating a subclavian artery to pulmonary artery anastomosis (Fig. 36). This was published in 1939 and with some disappointment, since it was not possible to produce an elevated pulmonary arterial pressure by such an anastomosis.¹⁶ However, some seven years later, when Helen Taussig approached him about the need to augment blood flow to the lungs in children incapacitated with dyspnea and cyanosis as a result of pulmonary stenosis, he recalled these experimental observations and

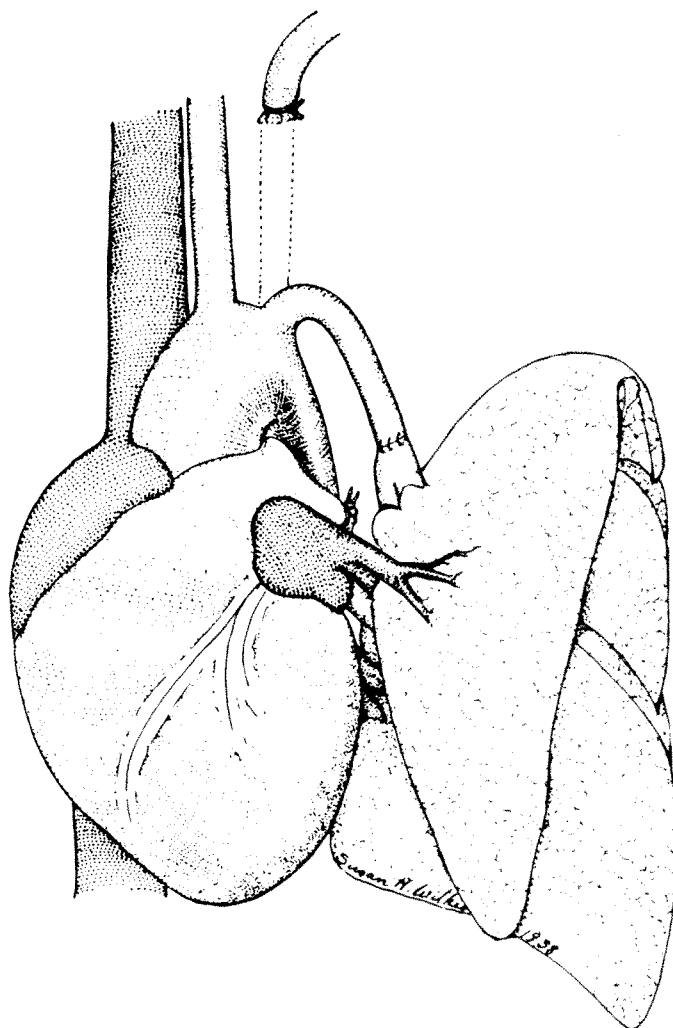


FIG. 36. Drawing showing original method of constructing an anastomosis between left subclavian and left pulmonary artery. (From J. Thoracic Surg., 8:525, 1939.)

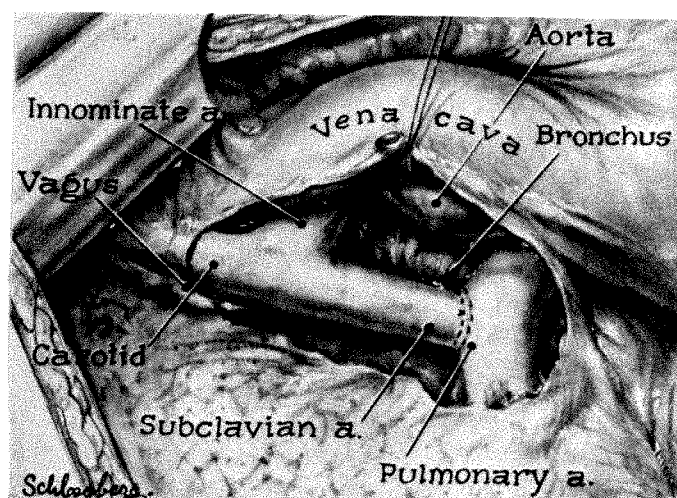


FIG. 37. Illustration of subclavian-pulmonary anastomosis (Blalock-Taussig operation) for pulmonic stenosis. (From Sabiston, D. C., Jr. and Blalock, A.: *The Tetralogy of Fallot, Tricuspid Atresia, Transposition of the Great Vessels, and Associated Disorders*. In: Derra, E., ed.: *Encyclopedia of Thoracic Surgery*. Vol. II. Heidelberg, Springer-Verlag, 1959.)

undertook the identical procedure in a severely ill 15-month-old patient on November 30, 1944 (Fig. 37). The result was superb and from that time forward, cardiac surgery began a period of remarkable progress.

In 1947, Dr. Blalock was invited to Guy's Hospital for a month's visit to introduce cardiac surgery in the British Isles. Concerning his impression of that visit, Evarts Graham was to say of him in a letter to President Isaiah Bowman of the Johns Hopkins University:

Dear Mr. Bowman:

I wish you could have been with me in London last month to have seen the acclaim which Alfred Blalock received. It did my heart good to see it. I could not help recalling some of the correspondence and conversations which you and I had about him a few years ago when he was being considered for his present post. I have always been sure of his ability and I have always been confident that he would go far in surgery if he had a good opportunity. I was tremendously proud of him in Europe, and I could not help getting a great deal of satisfaction out of the thought that my confidence had not been misplaced.

There has never been anything quite like Al Blalock's triumphal tour of Europe. The only thing that I can think of that remotely resembles it was a tour made by Marion Sims in the seventies or eighties of the last century. He had devised an operation and was received with great acclaim in the European capitals because of the success of his demonstrations. He came back loaded with honors from the various crowned heads. Al Blalock's tour has been no less dramatic and successful despite the fact that Europe is now down at the heel and there are few crowned heads left. The prestige of Johns Hopkins was enormously increased by Al's visit. All of us Americans were proud to claim him as a fellow American. His unassuming personality captivated everyone as much as his epoch-making surgical accomplishment.

Russell Brock,²³ the noted British cardiac surgeon, wrote of Dr. Blalock's visit to England in 1947:

... Dr. Blalock who presented his surgical contribution with his characteristic, apparently casual, drawl but really a forceful and incisive presentation of his brilliant and impressive results. The silence of the audience betokened their rapt attention and appreciation. The hall was quite dark for projection of his slides which had been illustrating patients before and after operation, when suddenly a long searchlight beam traversed the whole length of the hall and unerringly picked out on the platform a Guy's nursing sister, dressed in her attractive blue uniform, sitting on a chair and holding a small cherub-like girl of 2 and ½ years with a halo of blonde curly hair and looking pink and quite well; she had been operated on at Guy's by Blalock a week earlier. The effect was dramatic and theatrical and the applause from the audience was tumultuous. ... No audience could fail to have been convinced or satisfied by this summation and no one there could possibly forget it. ...

... the outstanding and important result of his visit was the firm introduction and launching of his operation in Great Britain and the Continent, acceptance of the immense possibilities of surgery in the alleviation of congenital heart disease in centres previously unconvinced and reluctant. The large numbers of visitors from the Continent and London for the International Meeting meant that they were also able to benefit and so the gospel was spread even more widely.

Upon his return from Europe, Dr. Blalock was to receive a letter from President Bowman which said:

I received such a heart-warming letter from Evarts Graham that I am enclosing a copy of it for your files. ... Happily the latter comes on a day when the Executive Committee of the Board of Trustees meets and I shall read it to them and state that I am sending a copy of it to each member of the full Board of Trustees.

... It is with growing pride and deep personal satisfaction that I have witnessed your growth in this environment and your steady advance to the first position in surgery in the United States.

If these sentiments seem to be extravagant, please remember that I do not see you as often as I would like and it is sometimes a little embarrassing on both sides when things like these are spoken by one man to another. And remembering your broad interest in the School of Medicine and the University and all of your kind attentions ... I want to subscribe myself on this special occasion as,

Affectionately yours,

With all of his achievements and international acclaim, those who worked with him closely knew Alfred Blalock's first love. On the occasion of his sixtieth birthday when a large throng from this country and abroad gathered to honor him, in his closing remarks he expressed his feeling and with unconcealed emotion saying, "With the exception of my family and close friends of my own vintage, my greatest pleasure in life has come from the resident staff. Most of them are here tonight, much to my delight, and all are fine gentlemen and superb friends." There can be no doubt that this feeling was thoroughly reciprocated on the part of his residents who knew him as exemplary teacher, investigator, clinical surgeon, and loyal friend.

In bringing these remarks to a close, let me emphasize the great surgical heritage which has been ours. Quite clearly, there is much reason to take pride in these accomplishments of our forebears, provided we accept them as challenges for future achievements. While it is a part of our nature, particularly in the South, to cherish tradition, we must recognize that its most poignant mean-

ing is the standard which it establishes. Clearly, high standards represent our best hope for the future. This concept and its potential relationship to surgery is beautifully expressed in a statement made by the London Times in its edition announcing the successful expedition of Sir Edmund Hillary in the conquest of Mount Everest: "In an age whose heart is dulled by the leveling of standards to the mediocre measure of the masses, here is an aristocracy that all can admire without envy."

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New Diagnostic and Therapeutic Techniques in the Management of Pyogenic Liver Abscesses

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An unexplained increase in the frequency of pyogenic liver abscesses of unknown etiology has, fortunately, been paralleled by significant advances in diagnostic and therapeutic methods. This report reviews experience with 14 patients operated upon at NYU Medical Center since 1971. Eight cases (57%) were cryptogenic. Other abscesses were associated with biliary disease (3); abdominal sepsis (2); and trauma (1). Abscesses were present on hospitalization in 12 patients. Clinical findings included fever (101-108 F), 100%; leucocytosis, 71%; anorexia and vomiting, 50%; localized tenderness and hepatomegaly, 50%; hypoalbuminemia, 86%; hypocholesterolemia, 78%; elevated SGOT, 71%; and elevated alkaline phosphatase, 43%. Technetium hepatic scintiscans showed focal defects in 10 of 12 patients (83%), but did not detect multiple abscesses in 2 of these. Hepatic arteriography performed in 10 patients was highly accurate, outlining single abscesses in 6 and multiple abscesses in 4. Furthermore, in one patient a false positive scintiscan was demonstrated by negative arteriography, confirmed by autopsy. In 4 patients, arteriography indicated an abscess in the posterior-superior area of the right hepatic lobe. With precise anatomical localization, a trans-thoracic approach permitted uncomplicated drainage in each case. This approach provides excellent exposure and direct drainage for abscesses in this area. An additional therapeutic adjunct in two patients, with 4 and 11 abscesses each, was postoperative intraportal infusion of antibiotics through the umbilical vein. Thirteen patients (83%) recovered, one dying from pulmonary embolism. Primary hepatic abscesses occur with increasing frequency. The methods described allow more precise preoperative diagnosis and direct surgical drainage.

PYGENIC LIVER ABSCESSES remain a significant diagnostic and therapeutic problem. The clinical findings are frequently nonspecific^{1,3,4,11,37,65,66} and the development of radioisotope hepatic scintiscanning has, therefore, been a significant diagnostic advance.^{4,45,84} Early diagnosis of hepatic sepsis may be especially difficult

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when abscesses occur without recognized antecedent illness. Recently, a surprising increase in the frequency of such "cryptogenic" abscesses⁴⁵ has further enhanced the importance of laboratory diagnostic methods.

The present study was undertaken to evaluate current diagnostic and therapeutic techniques because of both the reported continuing high overall mortality of liver abscesses^{3,4,7,15,25,44,45,66,68,72} and the increasing frequency of cryptogenic abscesses.

Material

Patient Population

The records of 14 patients undergoing surgical drainage of pyogenic liver abscesses at the New York University Medical Center between May 1971 and January 1974 have been reviewed. Eight patients were treated at Bellevue Hospital, 4 at the New York University Hospital and 2 at the Manhattan Veterans' Administration Hospital. There were 12 men and 2 women with an age range of 22 to 80 years (mean 49 years). Symptoms due to the liver abscesses led to hospital admission in 12 cases and developed during hospitalization in only 2 patients.

Etiology

In 8 cases (57%) no cause for the development of liver abscess could be detected. Liver abscesses were associated with biliary tract disease in 3 patients and developed secondary to hepatic trauma, appendicitis and ulcerative colitis, each in one instance (Table 1). No evidence of *Entamoeba histolytica* infection was de-

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TABLE 1. *Etiology of Liver Abscesses*

Etiology	Number	Percent
Cryptogenic	8	57
Biliary tract disease	3	21
Portal vein sepsis (Appendicitis, ulcerative colitis)	2	14
Trauma	1	7

ected in any patient. Two patients with cryptogenic abscesses had diabetes mellitus.

Clinical Features

Initial symptoms included fever (79%), general malaise (64%), anorexia or vomiting (50%), chills (36%), and right upper quadrant pain (36%). The most common relevant findings on physical examination were fever (100%), hepatomegaly (50%) and right upper quadrant tenderness (50%) (Table 2). In the 12 patients whose hospital admission was prompted by findings related to liver abscess, the admitting clinical diagnoses were: "fever of unknown origin" in seven, and "acute cholecystitis," "viral syndrome," "ulcerative colitis," and "pneumonia," each in one instance. One patient, who was evaluated initially at another hospital, was referred for management of a "liver tumor."

During the initial period of evaluation, all patients were febrile with temperatures of 101-108 F. Hypotension, with systolic blood pressure below 100 mm Hg, occurred in 4 patients (29%).

Laboratory Evaluation

The results of preoperative hematologic and biochemical evaluation are summarized in Table 3. Some degree of anemia was present in 57% of patients, and this was severe in 29% of cases. Leucocytosis was frequent, but not universal, being recorded in 71% of patients. The prothrombin time was elevated in 2 patients but was markedly abnormal in only one instance. Abnormal platelet counts were recorded in 45% of cases, with thrombocytopenia in 27% and thrombocytosis in 18%.

The most frequent findings on biochemical evaluation of liver function were hypoalbuminemia (86%), and

TABLE 2. *Clinical Features of Patients with Liver Abscesses.*

Symptoms	Number	Percent
Fever	11	79
Malaise	9	64
Anorexia or vomiting	7	50
Chills	5	36
Right subcostal pain	5	36
Signs		
Pyrexia (101-108 F)	14	100
Hepatomegaly	7	50
Right subcostal tenderness	7	50
Hypotension (>100 mm Hg)	4	29

TABLE 3. *Hematological and Biochemical Findings in Patients With Liver Abscesses.*

Laboratory Values	Proportion of Patients	Percent
Hematocrit	<35% 4/14	57 29
White Blood Cell Count	<30% 10/14	71
Prothrombin Time	>10,000/cu mm 2/12	17
Elevated	>15 seconds 3/11	27
Platelet Count	<175,000/cu mm 2/11	18
	>450,000/cu mm	
Serum Albumin	<3.5 G% 9/14	86 64
	<3.0 G% 7/14	50
Serum Bilirubin	<2.5 G% 1/14	7
	>2.0 mgm% 2/14	14
	>1.5 mgm%	
Serum Glutamic-Oxaloacetic Transaminase	>40 S.F. Units 10/14	71
	>100 S.F. Units 1/14	7
Serum Alkaline Phosphatase-Elevated*	6/14	43
Serum Lactic Dehydrogenase-Elevated*	5/14	36
Serum Cholesterol	<140 mgm% 7/9	78

*Laboratory units changed during study period.

hypocholesterolemia (78%). Hypoalbuminemia was marked in 50% of patients. Elevation of serum glutamic-oxaloacetic transaminase level above the normal range was recorded in 71% of the cases, but this elevation was rarely greater than 100 Sigma Frankel Units percent. Serum alkaline phosphatase and lactic dehydrogenase levels were elevated in 43% and 36% of cases respectively. Clinical or laboratory evidence of jaundice was present in only one patient who had established biliary cirrhosis. Although no specific test was diagnostic, two or more of these biochemical tests of hepatic function were abnormal in every case.

Bacteriology

The bacteriologic findings are summarized in Table 4. Although a total of 56 preoperative blood cultures were recorded in 10 cases, positive cultures were obtained in only 4 patients. The organisms identified were *Fusobacterium girens*, microaerophilic *Streptococcus*, *Escherichia coli* and *Enterobacter*.

Aerobic and anaerobic cultures were taken from the abscesses at the time of operation in all cases and identified organisms in 10 patients. Bacteria were seen on gram smear in one patient whose cultures were reported sterile. The bacteria identified were predominantly enteric and anaerobic organisms were cultured in 5 cases.

Radiology

Initial chest radiographs were normal in 9 cases (64%).

TABLE 4. *Bacteriological Findings on Blood Culture and Anaerobic and Aerobic Cultures of the Abscess Cavities.*

Etiology		Blood Cultures	Organism	Smear	Abscess Culture
		Positive/Total			
1	Biliary Disease	0/5	—	Gm Neg Rod Gm Pos Cocci	E. coli Enterococcus
2	"	—	—	Gm Neg Rod Gm Pos Cocci	E. coli
3	"	0/6	—	—	Klebsiella Enterococcus Peptostreptococcus Proteus vulgaris Proteus morgani E. coli Hemolytic Anaerobic Streptococcus Non-hemolytic Anaerobic Staphylococcus Streptococcus viridans
4	Ulcerative Colitis	4/7	Fusobacterium girens	Gm Neg Rods Gm Pos Cocci	Enterobacter
5	Appendicitis	0/4	—	—	No Growth
6	Trauma	3/3	E. coli Enterobacter	—	Anaerobic Hemolytic Streptococcus Int. coli aerogenes No Growth
7	Unknown	—	—	—	Anaerobic Diptheroids Staphylococcus aureus
8	"	2/6	Microaerophilic Streptococcus	Gm Pos Cocci	Bacteroides
9	"	—	—	—	No Growth
10	"	—	—	—	No Growth
11	"	0/4	—	—	No Growth
12	"	0/4	—	Gm Neg Rod	No Growth
13	"	0/10	—	—	No Growth
14	(Diabetes)	3/7	E. coli	—	Enterococcus
	(Diabetes)				

Right pleural effusions were demonstrated in 3 (21%), right basal atelectasis in one and a right lower lobe infiltrate in one patient. Plain abdominal radiographs revealed radiolucent areas with air-fluid levels within the hepatic shadow in 2 patients (14%).

Preoperative hepatic scintiscanning was carried out using Technitium 99 m sulphur colloid in 12 patients (Fig. 1). Focal defects in uptake were identified in 10 of these 12 patients (83%), but the presence of multiple abscesses was not recognized in 2 of the 10 cases. No focal defect was recognized in 2 patients (17%).

Hepatic arteriography was performed preoperatively in 10 patients. Selective cannulations of the celiac axis and superior mesentery artery were carried out following percutaneous femoral artery catheterization using the Seldinger technique.⁵⁰ Fifty ml of Renografin-76* contrast material were injected and rapid sequence films taken over at least a 25 second period in the anteroposterior and right posterior-oblique projections. Single abscesses were identified in 6 and multiple abscesses in 4 patients, corresponding closely to the operative findings (Fig. 2).

In the 12 patients in whom admission was prompted by symptoms related to liver abscesses, the mean duration

of preoperative evaluation was 7.3 days (range 1-20 days). A preoperative diagnosis of liver abscess was made in

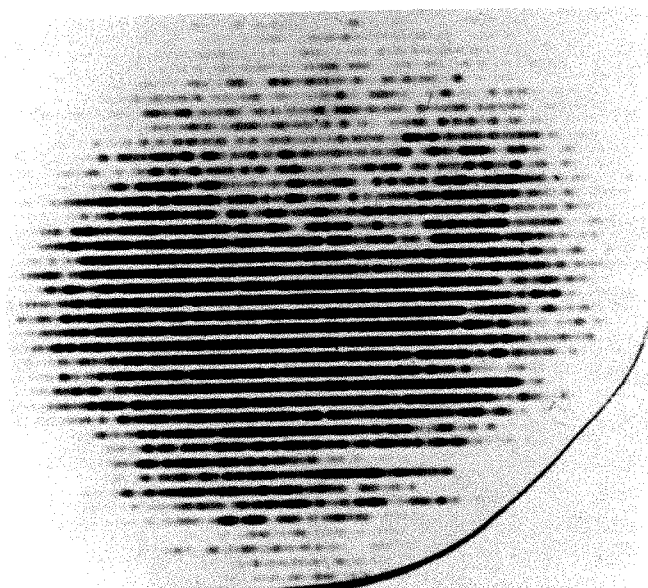


FIG. 1. Technitium 99 m S.C. hepatic scintiscan in the lateral projection from a patient (W.K.) with a solitary pyogenic abscess in the superior portion of the right hepatic lobe. There is a decrease in isotope uptake in the affected area. The solid line indicates the inferior and anterior costal margin.

*Renografin-76—Squibb & Sons, E.R. (Meglumine Diatrizoate and Sodium Diatrizoate Injection)

11 cases. In the 3 other patients, laparotomy was undertaken with the diagnosis of acute cholecystitis in one, and right subphrenic abscess in two instances. The first of these patients underwent emergency laparotomy within 24 hours of admission because of progressive right upper abdominal signs. The other two patients were explored because of fever, leucocytosis and right upper abdominal tenderness which followed operations for a gunshot wound of the liver, stomach, jejunum and right colon and for an extra-hepatic biliary stricture.

Treatment

Preoperative antibiotics were administered to all patients, but frequent changes in antibiotic regime reflected early diagnostic confusion.

In 8 cases, surgical drainage was carried out prior to January 1973. A transperitoneal approach was used in 6 of these patients, and a right subcostal, extraperitoneal approach was employed in 2. Difficulty was encountered in obtaining adequate exposure and direct drainage of abscesses in the posterior or superior aspects of the right hepatic lobe using these approaches. Therefore, a transthoracic transpleural approach was used in 4 of the 6 cases drained after January 1973, and 2 were drained transperitoneally. In all patients drained by the transpleural approach, preoperative hepatic arteriography had demonstrated abscesses confined to the posterior or superior portion of the right hepatic lobe.

In the transthoracic approach (Fig. 3), the ninth, tenth or eleventh rib was resected, depending upon the arteriographic findings. After the pleural cavity was entered, an intercostal tube was introduced into the fifth intercostal space in the anterior axillary line. The dome of the liver was gently palpated through the diaphragm, and the area of abscess was identified. The diaphragmatic pleura was sutured to the parietal pleura around the edge of the thorotomy incision using a continuous chromic catgut suture. The diaphragm was then opened and the abscess was unroofed. Samples of pus were taken for aerobic and anaerobic culture and the abscess wall was biopsied. Multiple soft rubber Penrose drains were introduced and the thorotomy incision was loosely approximated around the drains.

Postoperatively, broad-spectrum antibiotics were administered systemically in all cases, and, when possible, were chosen on the basis of the sensitivities of the organisms isolated on culture. In two patients, with 4 and 11 abscesses respectively, antibiotics were administered by way of catheters introduced into the reopened umbilical vein.⁶⁴ In these patients, the round ligament of the liver was identified in the edge of the falciform ligament. The lumen of the umbilical vein was reopened by passage of Bake's dilators and a small silastic catheter was introduced into the portal vein. Postoperatively, antibiotics

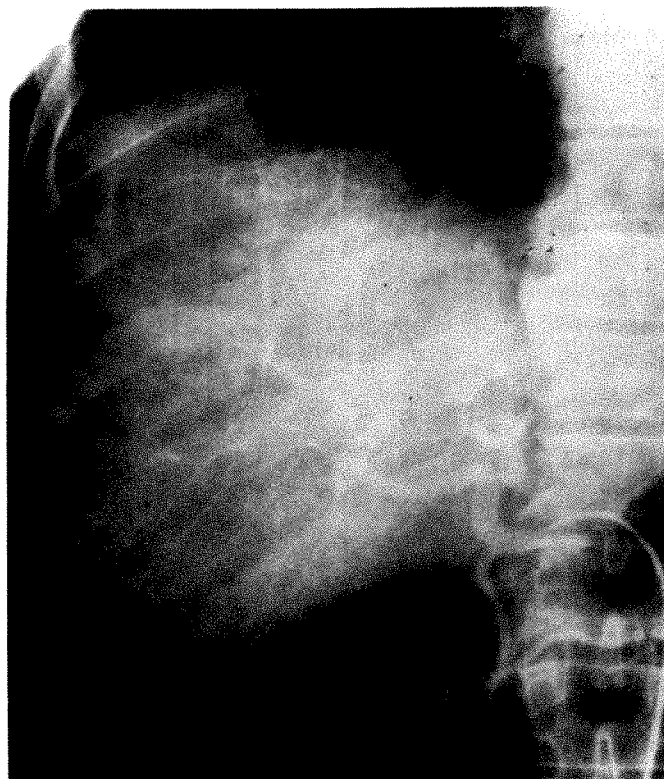


FIG. 2. Hepatic arteriogram in the anterior-posterior projection from a patient (W.K.) with a solitary pyogenic abscess in the superior portion of the right hepatic lobe. An avascular defect, with stretching and displacement of surrounding vessels and a surrounding vascular blush is demonstrated (arrow).

were administered by way of these catheters for 2 to 6 days.

Operative Findings

At operation, single abscesses were identified in 9 patients and multiple abscesses in 5. In 10 patients the abscesses were confined to the right hepatic lobe. One patient, with biliary tract disease, had a solitary left hepatic abscess and one patient had multiple bilateral abscesses of undetermined etiology. Five cryptogenic abscesses were single and 3 were multiple.

Associated subphrenic abscesses were encountered in 4 patients. The subphrenic abscesses were related to a gunshot wound and appendicitis in one case each, and to leakage from the hepatic abscess in two cryptogenic cases. In one of these patients, the subphrenic abscess was related to a previous percutaneous needle aspiration of the abscess.

Abdominal exploration, which was carried out in 8 cases, led to the identification of the previously undiagnosed, probable etiology of the abscess in only one patient, who was found to have cholelithiasis.

Results

One patient died suddenly of massive pulmonary em-

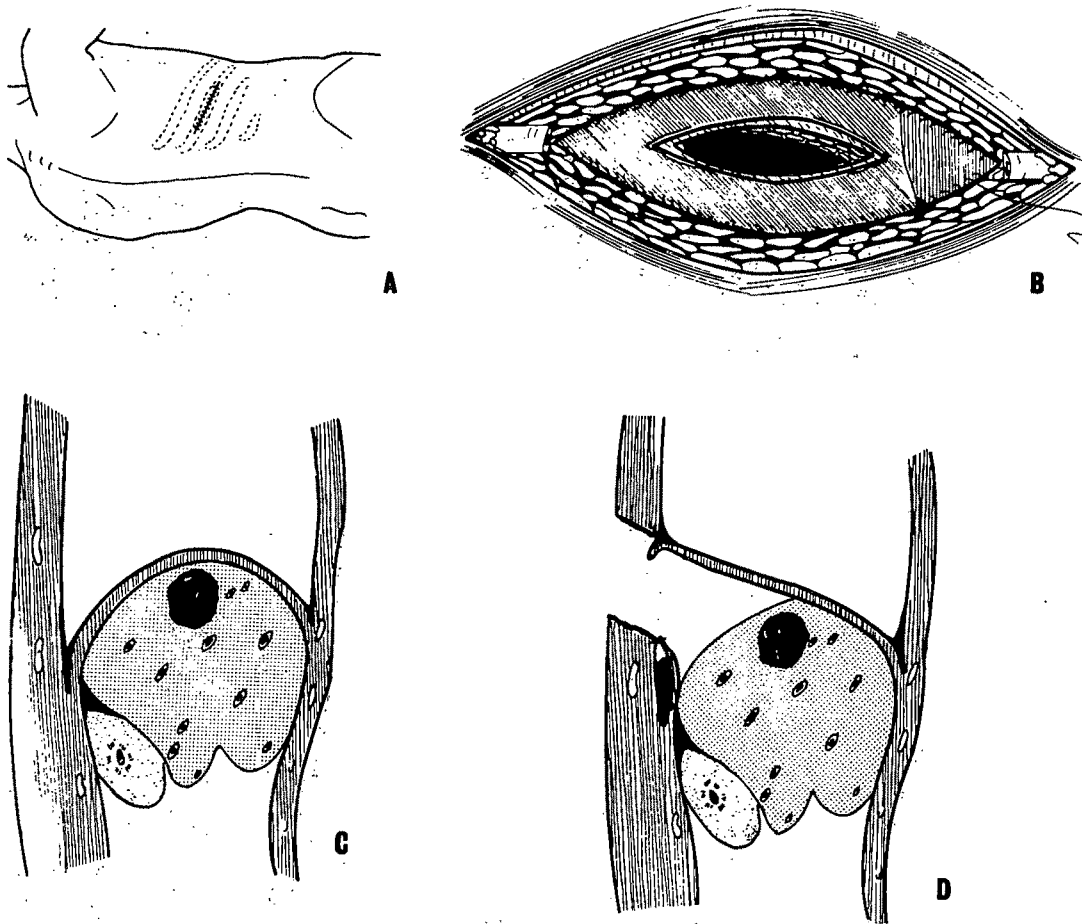


FIG. 3. Diagrammatic representation of the transthoracic approach to drainage of abscesses in the posterior or superior aspect of the right hepatic lobe. A: Incision; B: The diaphragm is sutured to the parietal pleura around the incision and the diaphragm is then opened to expose the liver; C: Sagittal projection, showing the relationships of the pleura, diaphragm and liver abscess; and D: Sagittal projection following posterior incision, suture of pleura and opening of diaphragm.

bolism on the fourteenth postoperative day without evidence of significant residual hepatic sepsis at autopsy. The remaining patients (93%) recovered and were discharged after a mean postoperative stay of 41.2 days (range 13 to 77 days). Major postoperative complications specifically referable to the hepatic abscesses or their treatment occurred in 3 patients. A recurrent left hepatic lobe abscess necessitated reoperation and redrainage in one and postoperative bleeding led to early re-exploration in one further patient. In one case, drained by a subcostal, extraserous approach, laparotomy was carried out on the third postoperative day because of progressive abdominal pain and tenderness. In this patient, infected ascites and a tense swollen liver were found and were attributed to possible hepatic vein thrombosis. Further operations during the postoperative period, which included total colectomy in one case and prostatectomy in two, led to additional prolongation of hospital stay.

The postoperative morbidity of single and multiple abscesses were the same, but the mean postoperative hospitalization of surviving patients with cryptogenic abscesses was 34.7 days, compared with 48.7 days in those with recognized predisposing disease. In patients drained by the transabdominal and extraserous ap-

proaches, average postoperative hospitalization was 46.6 days and 41.5 respectively. Morbidity was lower in those drained by a transthoracic approach with an average postoperative hospital stay of 31.5 days. Postoperative empyema did not occur.

The followup period for these patients is short, but the survivors have remained in good health except for one, who has known biliary cirrhosis. In patients with cryptogenic abscesses, no further etiologic evidence has been found since hospital discharge.

Discussion

Incidence

The true overall frequency of pyogenic liver abscesses is unknown, but, in autopsy studies, the reported incidence varies from 0.29% to 1.47%.^{57,72,78} Liver abscesses which were reported in 0.0077% of hospital admissions in 1938⁵⁷ were noted in 0.016% of admissions in 1974⁷² and several recent reported clinical series suggest a rising incidence.^{15,45,86}

The age of patients with pyogenic liver abscesses also appears to be increasing.^{15,18,44,78} In 1938, Ochsner⁵⁷ reported that the peak incidence of abscesses was in the third and fourth decades of life, but 64% of patients in the

present series were in the fifth and sixth decades of life, and the mean age was 49 years.

Pathogenesis and Etiology

Bacteria may reach the liver by way of the portal vein,^{19,53,77} biliary tree^{36,86} or hepatic artery^{15,57} or by direct extension from infection in adjacent organs,^{38,40} and the etiologic classification of hepatic abscesses is usually made on this basis.^{12,15,40,44,57,58,60,66,78} The frequency with which blood-borne bacteria normally reach the liver is uncertain.^{17,59,75,82} However, the hepatic reticuloendothelial system is remarkably effective in removing and destroying such bacteria,¹⁰ and the healthy human liver remains sterile.^{22,63} The pathogenesis of pyogenic liver abscesses involves a disturbance of the balance between bacterial contamination of the liver and hepatic resistance to infection. Although difficult to evaluate, it is probable that factors producing a focal decrease in hepatic resistance play a major role in the etiology of most liver abscesses.

The portal vein has been stressed by many authors as the source of hepatic sepsis.^{19,20,34,40,41,43,47,53,57,58,60,76} In such cases, hepatic resistance may be reduced by overwhelming sepsis, by portal venous thrombosis or emboli or by associated liver disease, such as occurs in ulcerative colitis.⁴³ Prior to the introduction of antibiotics, up to 48% of liver abscesses were attributed to infection in organs with portal venous drainage.^{40,57} In more recent series, portal vein sepsis has been implicated in less than 25% of cases.^{3,15,37,44,66,68,86} Portal pyelitis secondary to appendicitis was particularly common in earlier series^{19,34,46} and accounted for 34% of liver abscesses collected from the literature by Ochsner⁵⁷ in 1938. In reports published since 1960,^{3,4,37,44,58,60,66,68,86} appendicitis has been implicated in the etiology of less than 19% of liver abscesses. This improvement may reflect better management or a fall in the relative incidence of acute appendicitis.⁴⁶

Biliary tract disease was identified as the cause of 31.6% of pyogenic liver abscesses in a recent collected series¹⁵ and was present in 21% of our cases. The pathogenesis of these abscesses may be related to the presence of infection within the biliary tree together with impaired hepatic resistance resulting from biliary tract obstruction. A further possible mechanism was illustrated by one of our cases in which a large abscess deep within the hepatic substance appeared related to a small perforation in the posterior surface of the gall bladder.

Abdominal trauma has been emphasized in the pathogenesis of liver abscesses by several authors.^{37,58,66,72} Penetrating abdominal injury may cause direct bacterial contamination of the liver together with devitalization of hepatic tissue as was the case in one of our patients. Blunt abdominal trauma may also cause hepatic

tissue damage and predispose to the development of hepatic abscesses.⁷²

Hepatic arterial bacteremia is frequently implicated as the cause of liver abscesses that occur in association with infection in unrelated organs.^{15,58,78} This association has been reported in up to 40% of liver abscesses,⁵⁸ but since hepatic sepsis is a relatively rare complication of other infections,¹ it is probable that factors producing a decrease in hepatic resistance play a dominant role in the pathogenesis of these cases. Multiple microscopic liver abscesses are reported as an autopsy finding in patients dying with generalized sepsis.^{4,72,78} Although such abscesses may be included in analyses of autopsy series, they are not amenable to surgical treatment.

Focal liver injury is recognized as the dominant etiologic factor when pyogenic abscesses occur in association with hepatic tumor, tuberculosis, ischemia, immunologic rejection, amoebic infection or hydatid disease.^{3,39,40,44,51,69,72,78,80} Bacterial contamination in these cases is attributed to transient bacteremia.

No etiologic mechanism is identified in 2 to 46% of patients with liver abscesses.^{40,68} In the clinical experience reported by Lee,⁴⁵ the incidence of cryptogenic liver abscess has risen from 9% to 45% since 1965. The frequency of cryptogenic abscesses in series which include autopsy cases remains low.^{72,78} In such series, however, the relative incidence of cryptogenic abscesses may be decreased by the inclusion of hepatic sepsis occurring as a terminal complication of malignant disease and of microscopic abscesses occurring as the result of overwhelming sepsis. In three recent clinical reports,^{11,15,68} including 46 patients with pyogenic liver abscesses treated since 1961, no clear cause of the abscess could be detected in 20 cases (43%) and 57% of the present series of patients had cryptogenic abscesses.

The reason for this striking rise in the incidence of cryptogenic abscesses is obscure, but it is probable that unrecognized metabolic, ischemic or traumatic liver damage plays a dominant role in the pathogenesis of these abscesses. In this regard, an association of diabetes mellitus with liver abscesses has been noted,^{35,44} and diabetes was present in 2 of 8 patients with cryptogenic abscesses (25%) in the present series. The specific factors responsible for cryptogenic abscesses appear to be transient, since, to date, no recurrent liver abscesses have occurred in this group.

Bacteriology

Preoperative blood cultures were positive in only 40% of the present group of patients and gave an incomplete picture of the flora later identified from the abscesses (Table 4).

Bacteria cultured from the abscess cavities at the time of operation are usually enteric.^{44,72} The most frequent

organism identified has been *E. coli*, which has been reported to 18 to 64% of cultures^{4,7,12, 40,44,57,66,72,77,86} and was identified in 3 out of our 14 cases (21%). Other, frequently reported aerobic organisms include *Klebsiella*, *Enterobacter*, *Streptococcus viridans*, *Enterococcus* and *Staphylococcus aureus*, all of which were identified in the present group of cases.

Recently, the role of anaerobic organisms in the pathogenesis of liver abscesses has been emphasized.^{6,9,23,24,27,28,29,39,61,73,81} The failure to identify organisms in some cases of hepatic abscess may be related to inadequate anaerobic culture techniques. In support of this contention, organisms were seen on smear in one of our patients but could not be identified by culture. In recently reported series, no organism was identified in 12 to 18% of liver abscesses^{44,72} and cultures were sterile in 4 (27%) of the present series. Actinomyces⁸⁸ and pyogenic infection occurring secondary to amoebic hepatitis⁶⁹ has been reported, but these organisms were not identified on smear or biopsy in any of the present cases.

Clinical and Laboratory Features

The initial clinical findings in patients with pyogenic liver abscess are often nonspecific and an admitting diagnosis of liver abscess was not made in any of the present group of patients. Symptoms due to infection, including fever, anorexia and nausea were present in 11 patients (79%), and localized pain, tenderness or hepatomegaly were recognized in 10 cases (71%).

The most frequent abnormalities on routine hematologic and biochemical evaluation were leucocytosis, anemia, hypoalbuminemia, hypocholesterolemia and elevated serum glutamic oxaloacetic transaminase levels (Table 3). A number of authors have reported that jaundice is a frequent finding in patients with hepatic abscess,^{44,66,85} but serum bilirubin was elevated above 2 mg% in only one of our cases. Serum alkaline phosphatase levels may be abnormal in the presence of space-occupying lesions within the liver⁶⁷ but, in the present series, they were elevated in only 6 cases (43%), 2 of whom had known biliary tract disease. Measurement of the sulfobromophthalein retention has been reported to be useful in the diagnosis of pyogenic abscess^{4,15,44} but was not recorded in our patients.

Although two or more of the biochemical parameters listed in Table 3 were abnormal in each of our cases, the usefulness of laboratory evaluation of liver function in the diagnosis of liver abscess has been questioned.^{11,14,37} The significance of hypoalbuminemia and hypocholesterolemia in patients with chronic infection may be difficult to assess and Neale⁵⁵ has reported that biochemical liver function tests do not reliably distinguish between extra- and intra-hepatic infection. It is, therefore, unlikely that pyogenic liver abscesses are present in patients with entirely normal hepatic function. However,

relatively nonspecific abnormalities may be the only biochemical manifestation of liver abscess, and their presence requires further evaluation of this possibility by scintiscan and, possibly, arteriography.

Radiology

The occurrence of diaphragmatic elevation, basal pulmonary infiltrates or pleural effusions on chest radiograph may suggest upper abdominal pathology.^{33,37,54,65} Such abnormalities have been reported in 46-53% of liver abscesses,^{44,72,86} but were present in only 36% of the present series. Plain abdominal films may demonstrate a gas-containing cavity within the liver with air-fluid levels.^{21,32,33,35,37} This finding has been described as a radiographic curiosity, but was present in two (14%) of the present series of patients and provides clear evidence of hepatic abscess.²¹

The introduction of hepatic scintiscanning has been a major advance in the early diagnosis of hepatic abscesses.^{3,45,84} A study by Altemeier⁴ showed that in 21 patients treated prior to the introduction of scanning in 1965, the diagnosis was made prior to autopsy in only 19% and the overall mortality was 81%. In 18 patients treated since 1965, 78% were diagnosed antemortem and the overall mortality fell to 28%. Scanning can be carried out with minimal risk or discomfort to the patient^{8,76,84,85} and great accuracy has been reported in detecting hepatic lesions greater than 2 cm in diameter.⁷⁹ In the presence of sepsis, however, the uptake of isotope by the hepatic reticuloendothelial system may be impaired and the accuracy of scanning decreased.^{8,26,74} Technitium hepatic scintiscans were carried out preoperatively in 12 of our patients and showed focal defects in 10 cases (83%). In two of these cases with multiple abscesses, only a single defect was identified. In 2 other patients, hepatomegaly was reported with heterogeneity of isotope uptake noted in one. In one additional patient seen during this period, a false positive scintiscan was demonstrated by subsequent arteriograph and at autopsy. Recent reports^{48,49} on scintiscanning using Gallium 67, which is concentrated in areas of inflammation, suggest that this technique may improve the accuracy of scanning.

Visualization of the hepatic vasculature by hepatic arteriography has been suggested in the diagnosis of liver abscesses.^{4,11,21,44,56,65} The experience reported by Rubin⁷² suggests that the overall diagnostic accuracy of arteriography was no greater than that of hepatic scintiscanning but abscesses less than 1 cm in diameter were included in that analysis. In the present series of surgically treated cases, hepatic arteriography provided significantly improved accuracy in diagnosis and precision in anatomical localization of liver abscesses and was a valuable adjunct in the evaluation of these patients. The most significant arteriographic signs of liver abscess are: the presence of a mass effect with stretching and dis-

placement of the hepatic vessels; a complete lack of vasculature within the mass; and a surrounding blush of contrast material or "halo effect," which is best visualized during the capillary venous phase. The surrounding blush may be accentuated by the use of epinephrine angiography.⁵⁰ Angiography may not be able to distinguish between necrotic tumor and hepatic abscess and in one recent patient, this distinction could only be made by laparotomy.

Cholangiography in the present series of patients was helpful only in the evaluation of possible biliary tract disease.⁷⁰ The use of ultrasound has been recommended in the diagnosis of liver abscess³¹ but was not used in the present patients.

Treatment

The treatment of pyogenic liver abscesses includes the identification and correction of etiologic factors whenever possible, vigorous antibiotic therapy and drainage of the abscesses.

Ideally, antibiotic treatment should be determined on the basis of bacteriologic studies of the blood and abscess cavity. Penicillin or erythromycin and chloramphenicol have been recommended when bacteriologic data is not available.^{23,24,72} Bacteriologic studies in the present series indicated that 80% of organisms tested were sensitive to chloramphenicol and 78% were sensitive to gentamycin. Clindomycin has been recently recommended in the management of anaerobic infections³⁰ and was used in 5 of our most recent cases. The regional infusion of antibiotics increases their local concentration⁸⁷ and may improve their efficacy. Piccone⁶⁴ has reported that the administration of antibiotics by way of the reopened umbilical vein was a valuable adjunct in the successful treatment of 2 patients with liver abscesses. This technique was used in a further 2 patients in the present series, both of whom had multiple abscesses. One recovered uneventfully, and although the other died suddenly of pulmonary embolism on the fourteenth post-operative day, there was no evidence of significant residual hepatic sepsis at autopsy.

Some patients with microscopic hepatic abscesses may recover with antibiotic treatment alone. Most authors agree, however, that surgical drainage is mandatory whenever macroscopic hepatic abscesses are recognized.^{2,4,12,24,60,66,73} Recovery has been reported following closed or open needle aspiration and antibiotic treatment of solitary pyogenic liver abscesses.^{25,27,52,62} However, in one of our patients, percutaneous aspiration had resulted in a subphrenic abscess and, in larger series, the mortality of macroscopic abscesses which were not treated by open surgical drainage has been almost 100%.^{3,4,12,25,44,66}

The choice of surgical approach to drainage of liver abscesses has been the subject of controversy since

Ochsner's report in 1938⁵⁷ which recorded an increased mortality with transpleural or transperitoneal drainage and recommended an extraserosus approach. In 1969, however, an analysis by Longmire³⁷ of 26 cases of surgically drained abscesses, found that 2 of 5 patients (40%) drained by an extraserosus approach died, compared with 2 of 21 patients (10%) drained transperitoneally. The trans-serous, transabdominal approach provides the widest exposure of the liver and permits examination of the abdominal viscera for possible etiologic factors. This approach was used in 8 of the present series and no complications could be directly attributed to the choice of this approach. The possible etiology of the abscess was, however, identified in only one instance. For multiple scattered abscesses, or abscesses of the left lobe or anterior portion of the right lobe, this is the most practical approach. For abscesses in the superior or posterior aspect of the right hepatic lobe, the transabdominal approach provides poor exposure.¹²

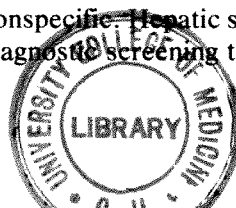
A transthoracic approach to the drainage of right subphrenic abscesses has been previously described^{13,16,42} and was applied, in two stages, to the drainage of hepatic abscesses by Rothenberg.⁷¹ Reported experience does not indicate any increased morbidity due to transgression of the pleural space.⁵ Following precise arteriographic localization, this approach was used in the present series to drain intrahepatic abscesses in the posterior or superior aspect of the right hepatic lobe in 4 patients. The approach provided excellent exposure, and permitted direct drainage and uncomplicated recovery in each case.

A subcostal extraserosus approach was used in only 2 of our patients. This approach may be satisfactory for abscesses confined to the right inferior portion of the right hepatic lobe. However, in the present series of patients, generalized peritonitis or empyema were not seen with the trans-serous approaches and it appears that with vigorous antibiotic therapy, contamination of the pleural or peritoneal cavities is not associated with the high mortality recorded in the preantibiotic era. The extraserosus approach, therefore, offers no apparent advantage at the present time.

Conclusions

Analysis of this recent clinical series of cases supports the observation that there is an apparent rise in the frequency of liver abscesses occurring without evident predisposing cause. Unrecognized factors which produce a decrease in hepatic resistance to infection may play a dominant role in the pathogenesis of such abscesses.

The diagnosis of pyogenic liver abscesses is rarely possible on clinical grounds alone. Biochemical evaluation of liver function is usually abnormal but frequently nonspecific. Hepatic scintiscanning provides an excellent diagnostic screening test and should be widely applied if



there is any question of possible hepatic abscess. The accuracy of diagnosis and precision of anatomical localization may be increased by preoperative hepatic arteriography.

Vigorous systemic antibiotic therapy is required in all cases and the transumbilical administration of antibiotics may be a useful adjunct in patients with multiple abscesses. Surgical drainage should be carried out whenever macroscopic pyogenic liver abscess is diagnosed. A transabdominal, transperitoneal approach provides wide exposure and permits satisfactory drainage for abscesses of the left lobe and anterior or inferior aspects of the right lobe. A transthoracic, transpleural approach provides improved exposure and direct drainage for abscesses confined to the superior or posterior aspects of the right hepatic lobe.

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DISCUSSION

DR. WILLIAM A. ALTEMEIER (Cincinnati): The cryptogenic nature of these abscesses is exceedingly interesting, and there is no question that the number occurring without any recognizable primary source is increasing. One of the reasons is that the primary episode of infection may precede by one to three months the development of the hepatic abscess to sufficient size, so as to make it recognizable or produce marked systemic symptoms.

In some of the patients we have studied there has been an antecedent episode of sepsis, followed by a latent period, and then a recrudescence of the symptoms preceding recognition of the abscess.

Dr. Spencer and his group have emphasized the obscure nature of this lesion, and this was true in the 51 patients with solitary abscess that we have operated upon. In this regard, we have changed the old adage of "Pus nowhere, pus somewhere, pus under the diaphragm or in the kidneys" to include "pus in the liver." In other words, if a patient comes in with the general signs of sepsis, but without localization, a scan and an arteriogram should be obtained to search for a possible liver abscess.

(Slide) This illustrates such a scan showing a large lateral abscess in the right lobe. This was found in a patient who had no localizing signs. He did have marked symptoms of generalized sepsis, with his temperature reaching 106 and being of a spiking nature.

(Slide) This arteriogram emphasizes the points characteristic of lower abscess which Dr. Spencer has made: absence of vascular markings in this area, a convexity of the branches of the hepatic artery on the surface of the expanding mass, and the halo effect which you can easily recognize.

(Slide) Here's a similar case in which the abscess was located more centrally, and the arteriogram shows essentially the same findings. Note again the halo effect.

(Slide) The bacteriology of these patients has been particularly interesting to me. The anaerobes have been found in greater numbers and frequency than the aerobes. Eight of the last 12 cases I have operated upon or done with my surgical residents during the past 22 months were associated with anaerobes only. In many of these instances the routine aerobic cultures were negative, where as anaerobic cultures grown in my Surgical Bacteriology Research Laboratory were positive.

Many of these anaerobes are killed by exposure to air in as little as three or four minutes. Their inoculation into special media within three or four minutes, or less, is essential if you hope to recover some of these bacteria. Furthermore, some are hemophilic and respond to special ingredients in media, including hemoglobin.

I should like to ask Dr. Spencer and his co-authors if the negative cultures could have been the result of delayed inoculation. This is an important consideration since our experience has emphasized the significance of anaerobic bacteria as a cause of these liver abscesses.

PROFESSOR J. PHILIP SANDBLOM (Lausanne, Switzerland): While listening to this very interesting talk, it occurred to me that I could point to another kind of liver abscesses; namely, the multiple or miliary liver abscesses, occurring in connection with ascending cholangitis, generally after a biliodigestive shunt. It is my long-standing suspicion that these biliodigestive shunts are not always unnecessarily maligned. To prove my point, I searched the literature for the scant reports of autopsies performed a long time after operation. Of 28 such cases, 21 had cholangitis. Many had miliary small liver abscesses, even without symptoms of frank cholangitis; just some fever and, certainly, signs of disease.

As those multiple small liver abscesses cannot be surgically drained, the best treatment is prevention by restricting the biliodigestive shunts to strict indications.

DR. WALTER J. BURDETTE (Houston): Our experience recently with a case of hepatic abscess, presumably pogenic, suggests that contemporary use of antibiotics, or other circumstance, may occasionally lead to chronic tumefaction of infectious etiology without the usual florid signs of acute infection. The patient was a young man, referred with a pulmonary complaint, who only admitted mild abdominal pain, when routine laboratory studies revealed the serum alkaline phosphatase to be elevated.

(Slide) Scintigram showed a large hepatic mass; and hepatic angiography in this area (indicating) outlined a discrete avascular mass in the left lateral hepatic lobe. It provided an accurate picture of the vascular pattern in the liver which proved useful during the resection of the lobe, which consisted in large part of a chronic abscess.

(Slide) This shows the arterial phase; and this the venous phase.

No offending organism was cultured intraoperatively, and we do not think it was for the reason just described by Dr. Altemeier. Recovery was complete after somewhat prolonged drainage. It would be of interest to obtain followup angiograms in some of these patients with acute abscess, to assess whether complete resolution always occurs after drainage. I hope the authors of this paper will present any information on that point, as well as their experience with chronic abscess.

DR. SAM E. STEPHENSON, JR. (Jacksonville): I always hesitate to rise to discuss a paper with a single case, but since the single case almost totals, in number of abscesses, Dr. Spencer's well-presented series of cases, I thought we might show it. This was also interesting in that sometimes you get into these things before you have time for all these preoperative studies, and this happened in this patient of ours.

The admission sheet started out: This 26-year-old black male presents with malaise, acute abdominal pain, and high fever. It goes on through the history and gets down to the physical, then after thorough questioning, it was revealed that the patient was a drug addict who had been mainlining.

(Slide) We operated for an acute abdomen and found a ruptured hepatic abscess. We found seven others on the surface that we drained at the same time, but then explored the common duct, left in a T-tube, and I think one can see this grapefruit tree-like arrangement. It looks like south Florida, with all the abscesses.

We drained as many as possible. The total at last count was 20-some. We still could not keep this patient afebrile, and finally had to resort to a right hepatic lobectomy.

These abscesses, as Dr. Spencer mentioned, can be multiple, and extremely difficult to drain. When one gets caught without all these nice preoperative studies, a T-tube with subsequent cholangiograms can be quite helpful in trying to localize them. What does not show on this slide very well, as most good x-rays tend to disappear, is that there was a stenotic area in the right main hepatic duct, and all the abscesses were proximal to that stenotic area.

DR. BEN EISEMAN (Denver): May I ask Dr. Spencer whether he has compared ultrasound scanning with arteriography and technetium scan in the diagnosis of liver abscess. We have thus detected five such abscesses, all of which were 2 cm or larger in diameter. It is, of course, a cheap and simple technique.

Many patients with liver abscess have underlying liver disease. Recently Drs. Norton, Moore and I have found that cirrhotics have depressed cellular immunity. Using 20 noninfected cirrhotics, we found such evidence by measuring IgG, IgM, Macrophage Inhibition Factor, and mitogenic response to Phythemagglutinin. Perhaps this plays a role in the etiology of such liver abscesses.

DR. HARRIS B. SHUMACKER, JR. (Indianapolis): First, may I say a word about the progress which has been made in the recognition of otherwise obscure hepatic abscesses? I hope you will not object to my illustrating this with a personal story. During the Centennial of Dr. Halsted's birth in 1952 I was serving as President of the Society of University Surgeons which met on this occasion in Baltimore. My wife suddenly became ill and was admitted to the Hopkins Hospital with a temperature of 106 and a shaking chill. For about two weeks she lay in bed being seen daily by the great professorial staff of that institution, having blood cultures at least once or twice each day, and shaking with chills and high fever. There were no other symptoms and no other

positive physical findings. This was long before the days of either scans or arteriography. Naturally no diagnosis could be made.

Finally she decided that if she were going to continue this course and ultimately die, she preferred to return home. And so, much against my good friend Al Blalock's advice, I took her back to Indianapolis. A few days later as I passed her room she saw me and called me in and said: "Harry, come here. For the first time I have a symptom besides a chill. I have pain in my right shoulder."

An x-ray showed nothing more than a liver which was at the upper limit of normal in size. The next day it was a little larger. That day, for the first time, cultures which had been growing for weeks were positive for streptococci.

My second comment relates to the transthoracic method of drainage. This was 23 years ago. One of my colleagues, Dr. Battersby, resected an appropriate segment of rib, packed it for a few days, which was customary at that time instead of the nice suture technique which Dr. Spencer mentioned, a few days later drained it, and she was soon entirely well.

Through my close association with the clinic at Leeds, I learned quite a number of years ago that Mr. Geoffrey Wooler had found that one could, after resecting a rib, suture the two layers of the pleura, or the two layers of the pleura and the capsule of the liver and seal off the pleural space. This enabled one to drain directly in one stage sub-diaphragmatic abscesses that lay between the dome of the liver and the diaphragm and liver abscesses located in this area. We adopted this technique quite a few years ago, both for drainage of liver abscesses and for sub-diaphragmatic abscesses situated in this area. One of our residents, Irving Heimburger, together with Mr. Wooler, described this simple modification in the American literature some years ago. It was a splendid contribution.

I would certainly agree with Dr. Spencer that this is the most direct and effective means of draining abscesses in this area, and in no instance in our experience has it been attended with empyema.

DR. JOHN H. C. RANSON (Closing discussion): In answer to Dr. Altemeier, we reviewed our bacteriological techniques at the time of this study to see if they could be improved. In four of our patients we did not identify an organism, and the precise point suggested was identified as the weak point in our technique: delay in the culture, and the poor use of transport media were thought to be the probably source of the failure in those cases.

Dr. Eiseman mentioned the use of ultrasound in the diagnosis of liver abscesses. This has been recommended in the literature, but we have no experience with it.

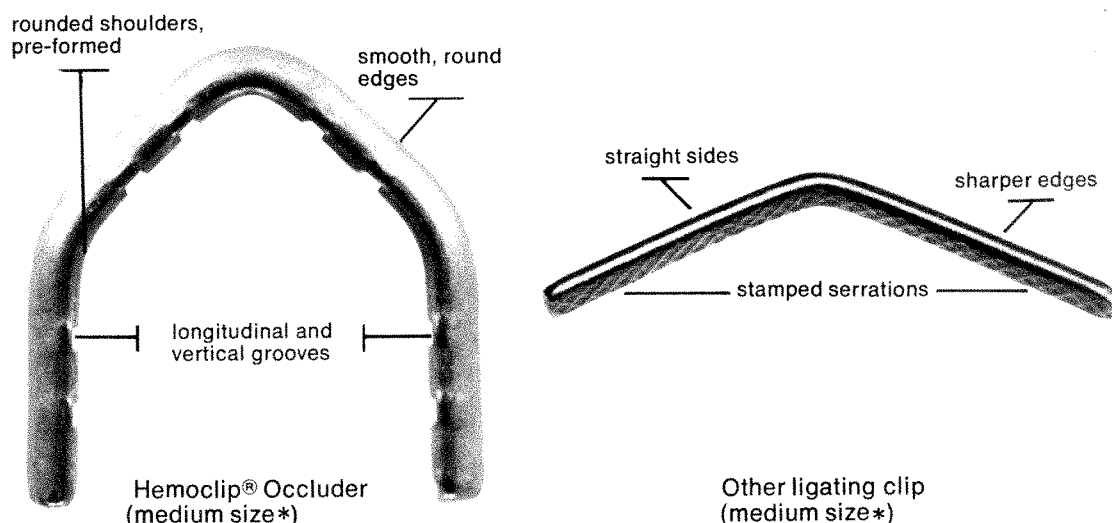
The apparent increase in incidence of cryptogenic liver abscesses seen in the present group of cases has also been noted in several other recent reports. In the past, most liver abscesses were associated with a recognized focus of infection elsewhere, and the etiologic classifications have usually focused on the route by which the infection has spread to the liver. The frequency with which blood-borne bacteria reach the liver is uncertain, but the studies of Beeson and others have shown that the reticuloendothelial system of the normal liver is remarkably effective in removing and destroying such bacteria.

The pathogenesis of liver abscesses involves a disturbance of the balance between bacterial contamination of the liver and hepatic resistance to infection. Since no abnormal source of infection was apparent in patients with cryptogenic abscesses, it is probable that factors influencing hepatic resistance to infection, such as those mentioned by Dr. Eiseman, play a dominant role in their pathogenesis.

In the present review a search for such factors revealed only that diabetes mellitus was present in two of eight patients with cryptogenic abscesses. Whatever the factors responsible for the genesis of these abscesses, they appear to be transient, since to date no recurrent abscesses have occurred in this group.

In closing, I'd like to reemphasize that since the clinical and routine laboratory features of liver abscesses are often nonspecific, early diagnosis requires the frequent application of liver scanning, and perhaps ultrasound, as Dr. Eiseman suggested. In the present group of patients preoperative arteriography increased the accuracy of diagnosis and allowed precise anatomical localization. Surgical drainage should be by the most direct route, since the extraperitoneal approach did not offer any apparent advantage.

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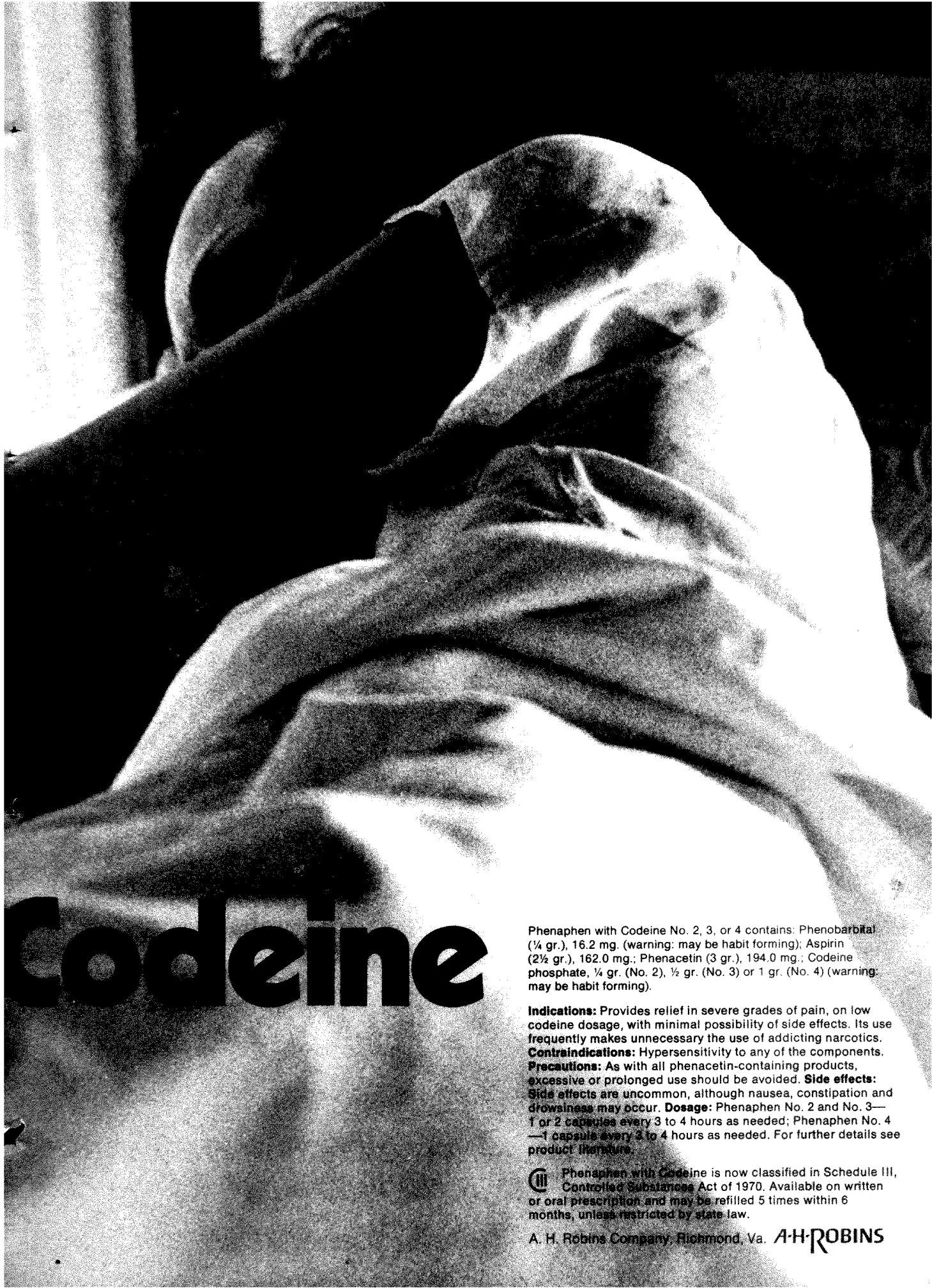
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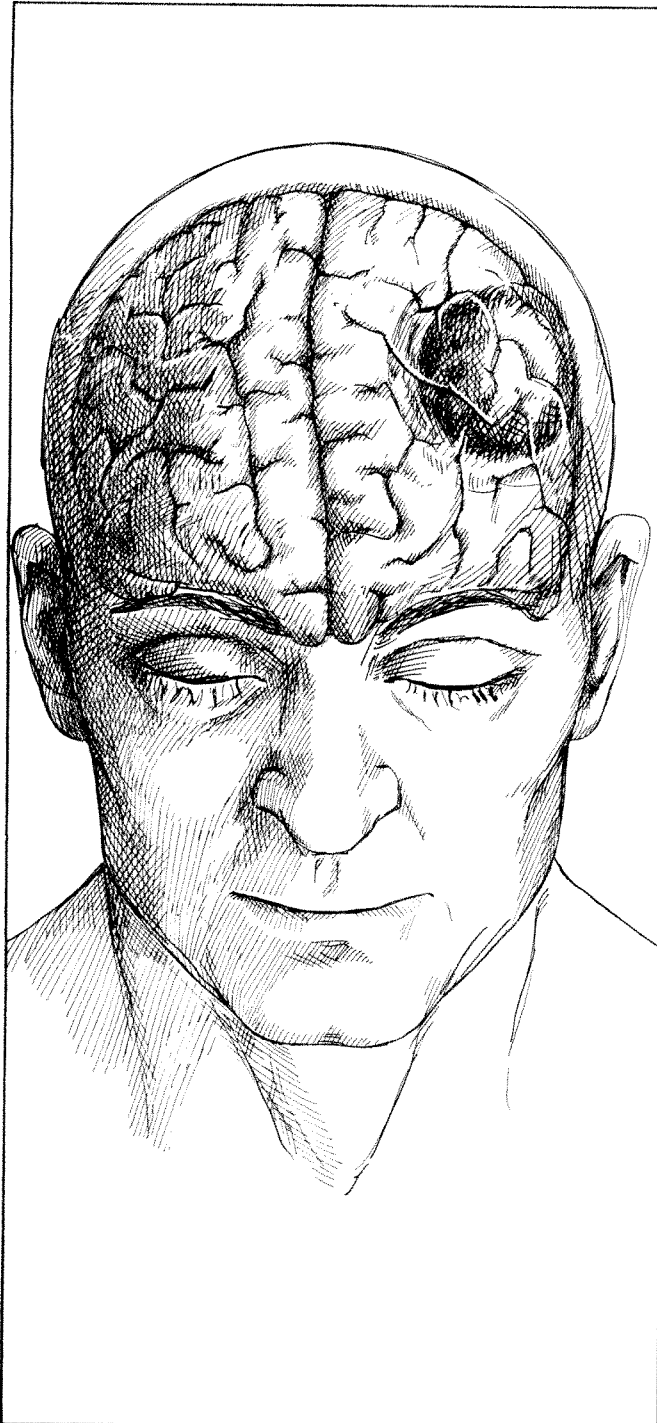
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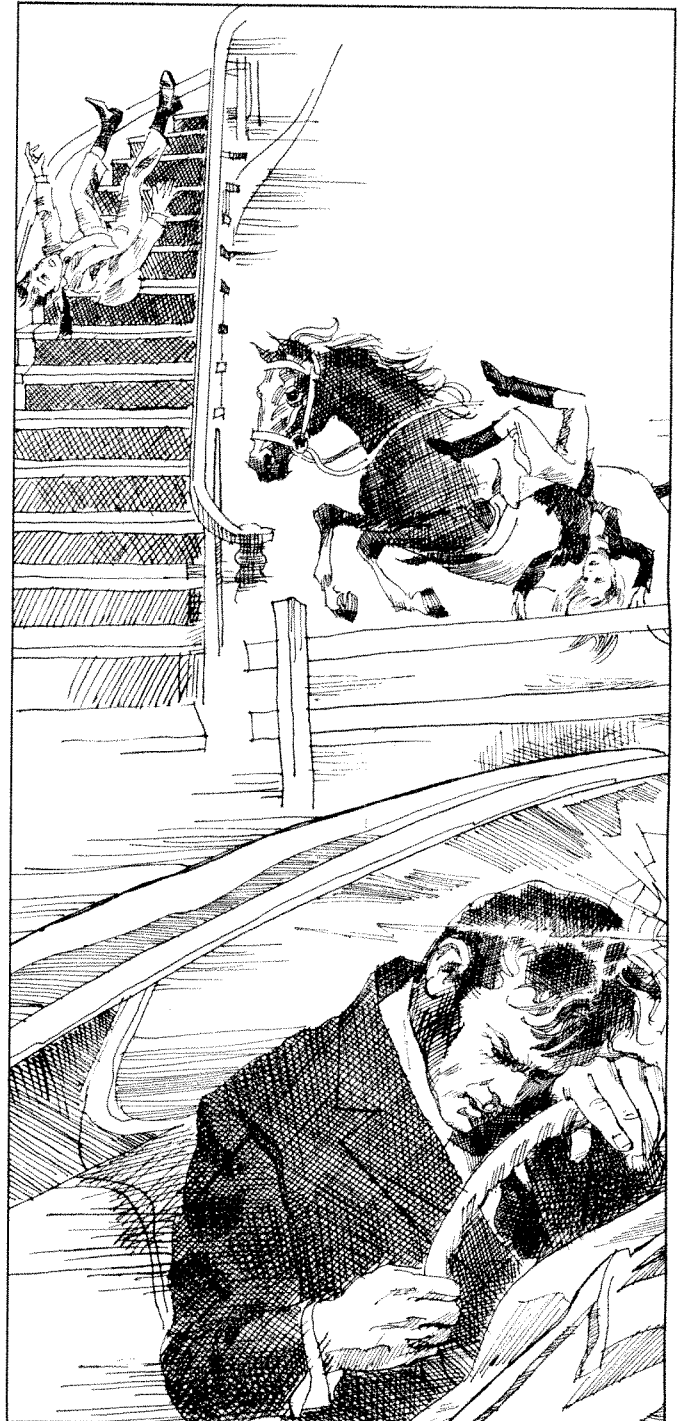
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cerebral

expect it as a possible complication of primary or metastatic brain tumor.

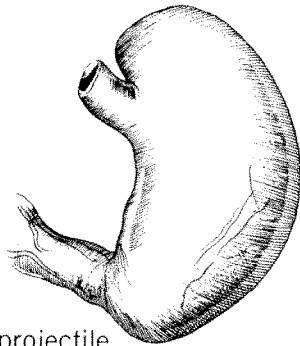


expect it in the presence of severe head injury.

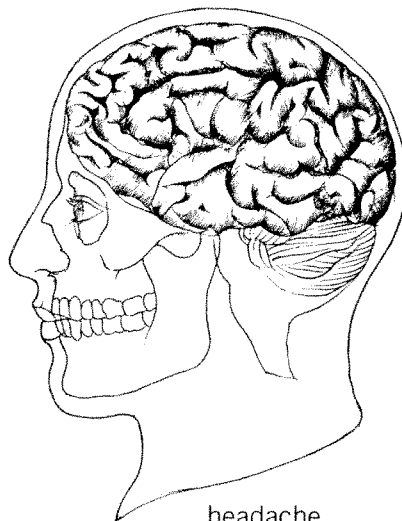


edema*

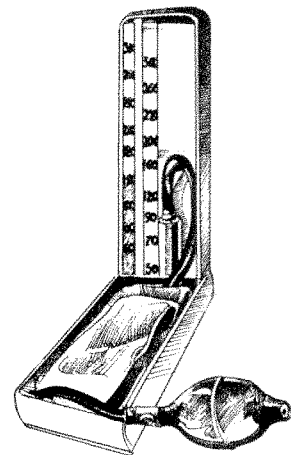
suspect it in the presence
of signs and symptoms such as these:



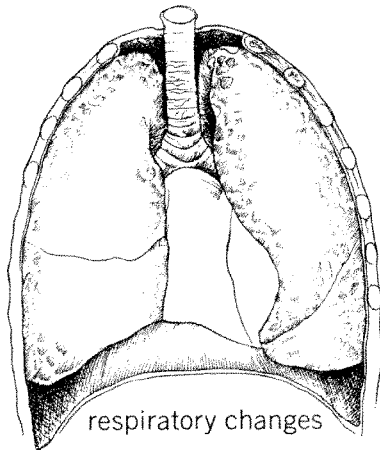
projectile
vomiting



headache,
altered consciousness

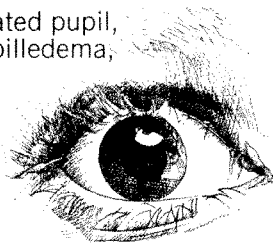


increased
blood
pressure

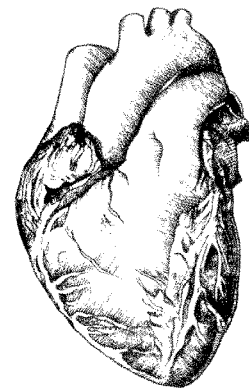


respiratory changes

dilated pupil,
papilledema,



unilateral or bilateral
abducens palsy



bradycardia

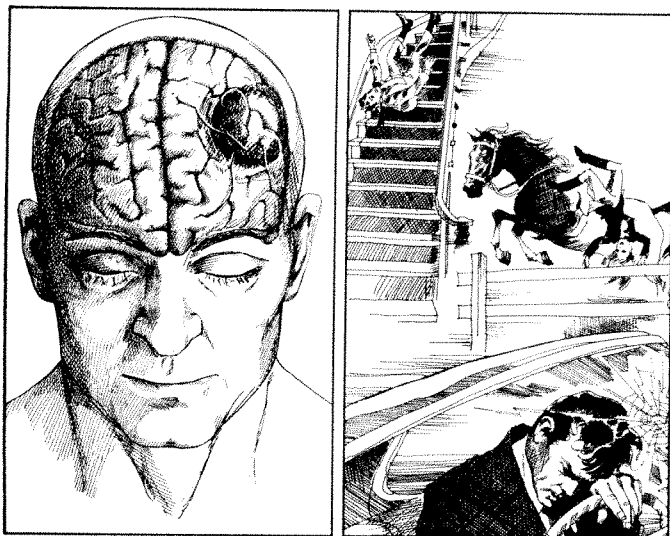
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Ritchie WP: The emergency care of cerebral injuries, J Lancet 86:255, June 1966.

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Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteroids; dietary salt restriction and potassium supplementation may be necessary. All

corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden re-appearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads;

pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

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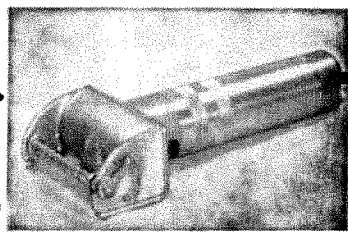
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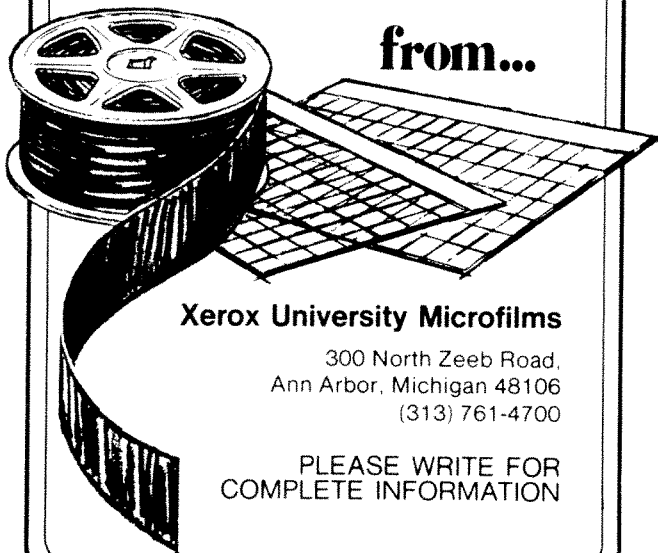
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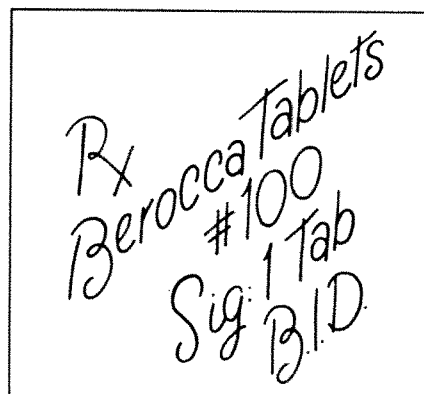
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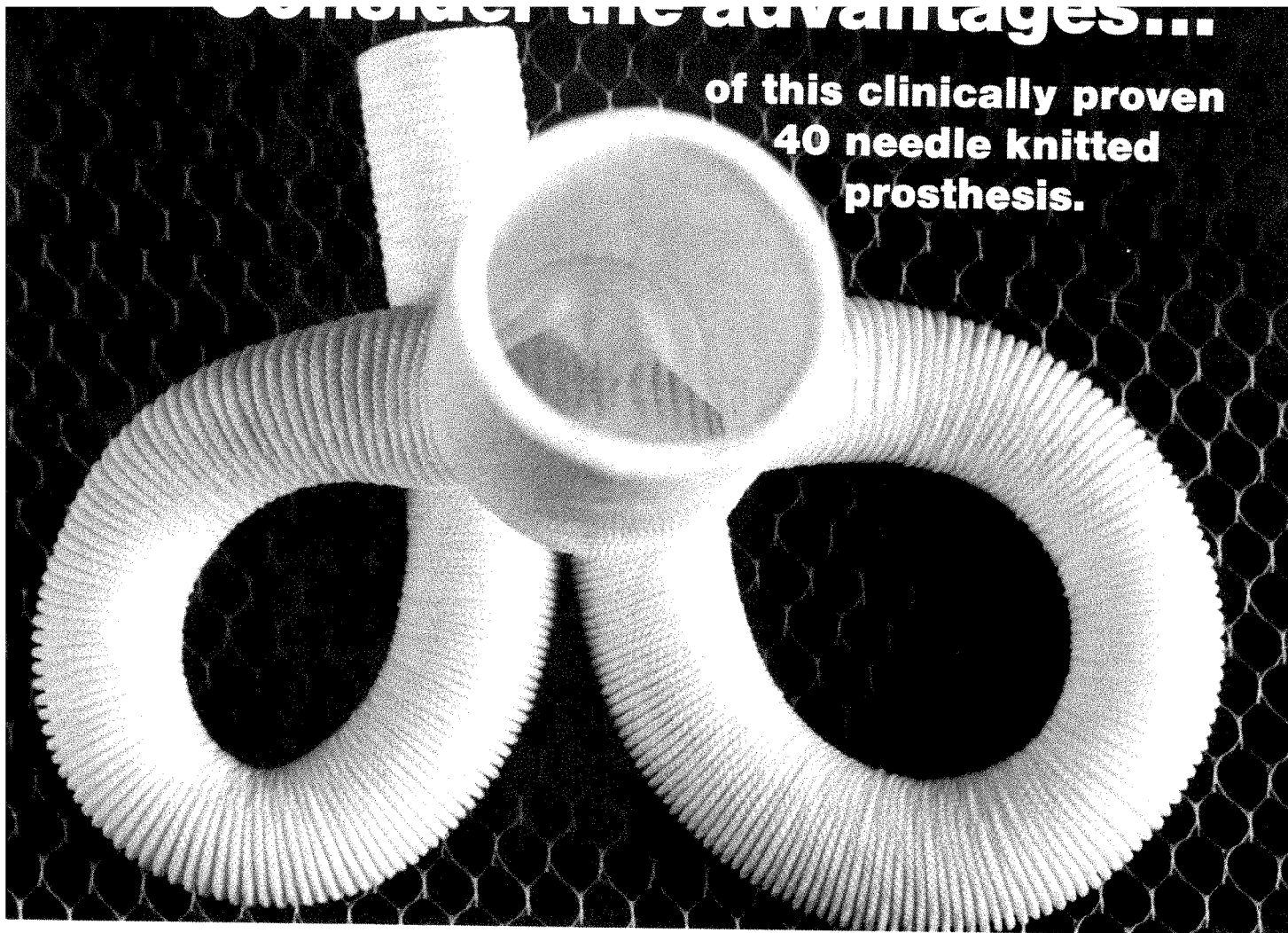
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Traumatic Injury to the Portal Vein

KENNETH L. MATTOX, M.D., RAFAEL ESPADA, M.D., ARTHUR C. BEALL, JR., M.D.

Traumatic injuries to the upper abdominal vasculature pose difficult management problems related to both exposure and associated injuries. Among those injuries that are more difficult to manage are those involving the portal vein. While occurring rarely, portal vein injuries require specific therapeutic considerations. Between January, 1968, and July, 1974, over 2000 patients were treated operatively for abdominal trauma at the Ben Taub General Hospital. Among these patients, 22 had injury to the portal vein. Seventeen portal vein injuries were secondary to gunshot wounds, 3 to stab wounds, and 2 to blunt trauma. Associated injuries to the inferior vena cava, pancreas, liver and bile ducts were common. Three patients had associated abdominal aortic injuries, two with acute aorto-caval fistulae. Nine patients died from failure to control hemorrhage. Eleven were long-term survivors, including two who required pancreatoduodenectomy as well as portal venorrhaphy. Late complications were rare. The operative approach to patients with traumatic injuries to multiple organs in the upper abdomen, including the portal vein, requires aggressive management and predetermined sequential methods of repair. In spite of innumerable associated injuries, portal vein injuries can be successfully managed in a significant number of patients using generally available surgical techniques and several adjunctive maneuvers.

TRAUMATIC INJURIES to the portal vein rarely have been reported alone, although they have been cited among reports of injuries to the aorta and vena cava.^{1,9,14,17} Chisholm⁵ reported three cases of traumatic injury to the portal vein with two survivors, and Fish⁷ reported 38 patients with neoplasia or trauma involving the portal vein which required vascular reconstruction. The portal vein, surrounded by other major vessels, as well as the liver, duodenum, pancreas, stomach and colon, rarely is injured without extensive associated injury to surround-

From the Cora and Webb Mading Department of Surgery, Baylor College of Medicine, and the Ben Taub General Hospital, Houston, Texas

ing organs. This report summarizes experience with 22 such injuries over a 6½ year period.

Clinical Material

Between January, 1968, and July, 1974, over 2000 patients were treated operatively for abdominal trauma at the Ben Taub General Hospital in Houston, Texas. Among these patients, 22 were found to have injuries to the portal vein. Nineteen were male, and the average age was 29 years. Gunshot wounds accounted for 17 of the injuries, stab wounds for 3, and blunt trauma was the etiology in 2 patients. They received an average of 14.4 units of blood. Fourteen of the 22 patients had blood pressures lower than 80 mmHg systolic at the time of arrival at the hospital. All patients had one or more associated injuries (Table 1). Repair was accomplished by lateral venorrhaphy in 12 patients, and the portal vein was ligated in 4. In 4 patients the portal vein was clamped or packed during unsuccessful resuscitation and repair was not attempted. In one patient an end-to-end anastomosis was performed, and a portocaval shunt was done in one patient (Table 2). In three patients intracaval shunts were helpful in control of exsanguinating hemorrhage, and in two patients a pancreatoduodenectomy was required because of extensive associated injury to the head of the pancreas. Those organs most commonly injured in association with portal vein injury included the inferior vena cava, liver, pancreas, stomach, kidney and various vessels in close proximity to the portal vein (Table 3). Associated vascular injury occurred in 20 of the 22 patients, the inferior vena cava being the most commonly injured (Table 4). Three patients had associated abdominal aortic injuries, two with acute aorto-caval fistulae.

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TABLE 1. *Number of Associated Organs Injured*

Number of Injuries	Number of Patients
1	1 (0)
2	5 (2)
3	4 (3)
4	3 (2)
5	6 (3)
6	2 (0)
8	1 (1)

() = Survivors

Results

Eleven of the 22 patients survived portal vein injury. The most common causes of death among the 11 patients who did not survive were failure to control hemorrhage and disseminated intravascular coagulopathy, the latter secondary to multiple organ system injury, massive blood transfusions and accompanying hypothermia. Six of 7 patients who arrived with no discernible blood pressure died, while 4 of 7 patients who arrived with blood pressures less than 80 mmHg systolic died. Severity of injury to associated organs, rather than the number of associated organs injured, contributed most significantly to deaths (Table 1). All patients who had packing, clamping or ligation of the portal vein in an attempt to control blood loss during resuscitation died of massive associated injuries. Seven complications occurred among 6 of the 11 survivors (Table 5). These included pancreatic pseudocyst, cholangitis, and respiratory insufficiency in one patient each. All 11 surviving patients were doing well when last seen in the clinic.

Discussion

Oré,¹³ in 1856, observed that sudden occlusion of the portal vein resulted in death in the experimental animal. Deaths following acute ligation of the portal vein were thought to result from systemic hypotension and portal congestion,^{2,8} although, in the monkey, demonstrable collaterals rapidly developed with resultant survival.¹² In the human, ligation of the portal vein for both traumatic

TABLE 3. *Associated Injuries*

Injury	Number of Patients
Inferior vena cava	15
Liver	13
Pancreas	7
Stomach	6
Kidney	5
Renal Vessels	5
Superior Mesenteric Vessels	5
Aorta	3
Hepatic artery	3
Common bile duct	3
Small bowel	3
Duodenum	3
Spleen	2
Colon	2
Lung	1
Heart	1
Flail chest	1
Celiac axis	1
Hepatic vein	1
Gallbladder	1
Middle colic artery	1
Central nervous system	1

injury and following resection of tumor invasion has been reported.^{5,7}

The portal circulation, the principal afferent blood supply to the liver provides up to 80% of the oxygen transport to the liver.¹⁶ Child⁴ postulated that 80% of human subjects could tolerate acute occlusion of the portal vein, and provided experimental observations of physiologic events which occur with portal vein ligation. These included immediate drop in blood pressure to 30 mmHg with return to normal in 30 minutes, an immediate increase in portal vein pressure to 35 cm of saline, and a decrease in liver volume. He further observed that 10 days after ligation there were normal liver function tests with normal liver biopsy and no thrombotic episodes. There was subsequent development of collaterals in his experimental models, consisting of pelvic collateralization immediately, small hepatic hilar vessel collateralization in one month, and large hilar collateralization in 4 to 6 months.

TABLE 2. *Methods of Management*

Method	Number of Patients
Lateral Repair	12 (9)
Intracaval shunt	3 (2)
Whipple operation	2 (2)
Ligation	4 (0)
Clamped or Packed	4 (0)
End-to-end Anastomosis	1 (1)
Portacaval Shunt	1 (1)

() = Survivors

TABLE 4. *Associated Vascular Injury*

Injury	Number of Patients
Inferior vena cava	12
Renal vein	4
Inferior vena cava and aorta	3
Superior mesenteric artery	3
Hepatic artery	3
Superior mesenteric vein	2
Renal artery	1
Hepatic vein	1
Middle colic artery	1
Celiac axis	1

TABLE 5. *Complications Among Survivors*

Complication	Number of Patients
Pancreatic fistula	2
Subphrenic abscess	2
Pancreatic pseudocyst	1
Cholangitis	1
Respiratory insufficiency	1

Portal hypertension may develop following ligation of the portal vein, as demonstrated experimentally by Child.⁴ Patton¹⁵ described two patients with portal vein injuries treated with apparent ligation who later required decompressive procedures to relieve portal hypertension. Occasionally, late bowel infarction may occur following portal vein ligation in human subjects and this has been attributed to mesenteric venous obstruction.⁴

Fish⁷ reviewed 6 methods of reconstruction of the portal vein. These included lateral repair, end-to-end anastomosis, ligation, portacaval shunt, splenic vein to superior mesenteric vein anastomosis following ligation of the hepatic end of the portal vein, and prosthetic graft interposition. McClelland¹⁰ has recommended use of autogenous vein graft interposition, portacaval shunt and use of ligation if the general condition of the patient does not permit complicated reparative techniques. With extensive destruction of the portal vein, an alternative to portacaval shunt might be ligation of the portal vein and insertion of a superior mesenteric vein to vena cava shunt using a Dacron prosthesis. However, 4 of 5 patients reviewed by Fish⁷ who had portacaval shunts for portal vein reconstruction had either hepatic decompensation or encephalopathy. These late complications were not observed in patients with portal vein ligation alone.

When traumatic injury to the portal vein is encountered, a variety of treatment options are available. A flexible but programmed approach should be employed. lateral venorrhaphy is preferred, if possible, with portal-systemic decompression an alternate method of management. Should extensive associated injuries be present, ligation, clamping or packing of the portal vein may allow for salvage of the patient. Ligation of the portal vein, although it may result in portal hypertension, is compatible with patient survival in approximately 80% of the cases.⁴

As associated injuries are common,^{5,9} early assessment of the injury, control of hemorrhage by available techniques including intercaval shunt,³ temporary occlusion by Fogarty balloons¹⁰ and the use of vascular clamps may be helpful while repairing other more crucially injured organs or vessels. Since portal vein injuries usually are associated with other major vascular injuries, a search should be made for such an injury in all cases of upper abdominal vascular trauma.¹¹ Likewise, in those

patients in whom a portal vein injury is found, assessment of all vessels in close proximity is mandatory, as unrecognized injury may result in delayed appearance of vascular fistulae.⁶

Adjunctive techniques may be helpful in the management of patients with portal vein injuries. Intracaval shunts aid in control of hemorrhage in the patient with massive liver, hepatic vein, and suprarenal vena caval injuries which occur in association with portal vein injuries.³ Fine screen filtration* of banked blood to reduce post transfusion pulmonary insufficiency and autotransfusion of shed blood have been useful in the management of patients with major vascular trauma.¹¹ Consideration of factors such as these and an aggressive sequential plan of management should allow salvage of a significant number of patients with portal vein injury.

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DISCUSSION

DR. H. HARLAN STONE (Atlanta): Over a 16-year period, 21 patients with portal vein injury and three with both the portal vein and the superior mesenteric vein injured, were explored at Grady Hospital in Atlanta. In these 24 patients, an additional 28 major vascular injuries were noted and such accounted for most of the death.

(Slide) Of 21 patients with a portal vein injury alone, there were 15 deaths. Our mortality was almost double what has been described by the group at Houston with no survivors when both the superior mesenteric vein and the portal vein have been injured. The usual cause of death was hypovolemic shock; yet a number of patients died from bleeding diatheses as a consequence of massive transfusions.

There are two main problems to be considered in the postoperative period. One is splanchnic pooling. This occurs if the portal vein has been ligated, as frequently needs to be done, or when thrombosis complicates a lateral repair.

(Slide) This patient had a lateral phlebostaphy of the left branch of the portal vein. A postoperative angiogram demonstrated that it was thrombosed, while the right branch was still open. Such usually happens within only a few hours of the repair. No patient with reconstruction of portal flow had vein patency when we had the opportunity to examine the vessel later at autopsy or by angiography. Thus, splanchnic pooling becomes an important consideration and may demand massive amounts of extra intravenous fluid post-operatively.

Secondly is the horrible situation where both hepatic artery and portal vein have been injured. Under these circumstances, we generally have elected to reconstitute the portal vein, rather than the hepatic artery. It is most easily done by anastomosing a segment of saphenous vein into the stump of the portal vein proximally, and then bringing that down to the side of the superior mesenteric vein. If one tries to reanastomose the portal vein end to end, exposure is lost as the two ends are pulled together.

DR. WALKER REYNOLDS (Anniston, Alabama): I enjoyed the paper given by Dr. Beall with his emphasis on the multiplicity of injuries in association with the injury to the portal vein as the cause of the high mortality rate in these patients. I would add that the location of the wound of the portal vein itself also has considerable importance in the difficulty in handling this situation. I will report a case in which this was my number one problem.

A 37-year-old male was shot in the left cheek, right shoulder, and right anterior chest. When seen in the emergency room he was in borderline shock 98/68, and was prepared for operation with Ringer's lactate solution until blood was available. The wounds of entrance were in the right anterior chest wall, right shoulder, and face.

The patient was taken to the operating room where the abdomen was opened through a midline incision and due to the voluminous amount of blood we were unable at first to determine the source of bleeding. We knew that it was probably in the liver with an associated injury to a large blood vessel. We then resected the falciform ligament bringing the liver forward where we could see the bullet wound of entrance into the liver itself. The wound was large enough that we were able to introduce our finger into the track of the bullet through the liver to try to determine the direction of the injury which was found to be toward the caudate lobe and through the hilar structures of the liver. Therefore, we decided to pass a rubber catheter down through the path of the bullet so that we could follow the bullet track by having direct exposure in removing a wedge section of the liver with the apex toward the track of the bullet itself as we could see no other way of getting to the actual site of the bleeding. This was done with Allen clamps pointed toward the track using Mersilene retention sutures.

(Slide) This shows the portal vein and the wound of entrance which was just above the gallbladder. The bullet came out at the hilar region at the junction of the portal vein and the right and left hepatic branches. The gallbladder was attached to the wedge of the liver which was removed to visualize the origin of the hemorrhage.

(Slide) This shows a much wider liver resection than necessary in this patient, but illustrates the fact that we were able to use hemoclips to save time with bleeders as we were working against time due to the severe hemorrhage.

We found out immediately that the medium hemoclip was not large enough to occlude the liver vessels; therefore, we used the large size hemoclip which occludes 4-11 mm vessels. We then proceeded down the track until we reached the portal vein division of the hepatic branches where we found the rent in the portal vein. We immediately

put pressure in the area, released it and gradually occluded the area with a large hemoclip which was successful in controlling the hemorrhage.

I am certain that we would not have been able to repair the rent in the portal vein with a suture ligature as the bleeding was too rapid and the area would fill with blood before one could place the suture ligature. We did use an additional arterial suture to help repair the area once the bleeding was under control. Once we had opened the abdomen and the severe hemorrhage noted, the patient went into shock and remained in shock throughout the course of the operation.

We were working against time during the entire operation. At one time there was no blood pressure for 15 minutes. The bullet itself had previously been removed having been found in the omentum. There was also an injury to the pancreas. The area was drained and the patient closed.

He was still in shock even though he received 12 pints of blood during the operation. However, on reaching the recovery room, the blood pressure returned to a normal range, and he followed an almost uneventful recovery with the nasogastric suction being removed the third day. He was carried on antibiotics Lincocin and Chloromycetin and otherwise followed conservative measures during his hospital stay.

(Slide) This shows the technique that we consider very valuable in reaching difficult places of bleeding by using direct pressure with one's finger and a large hemoclip to ligate the bleeding vessel. In this case, we do not know whether we completely occluded the portal vein or not. We did ligate a branch of the hepatic artery. The patient's SCOT went up to 176 but returned to normal range by the time of discharge. He was discharged on the 13th hospital day and has had no complications from his portal vein injury.

DR. W. ANDREW DALE (Nashville): The most significant portal vein injury which ever occurred was in 1894 and resulted in the death of the President of the French Republic at that time, Sadi Carnot, who was assassinated by an Italian anarchist. As sometimes happens, the long-term effects of this event eventually outweighed by far the immediate excitement which it provoked.

The inability of the senior surgeons of that time to repair the portal vein at once attracted the interest of a medical student. His name was Alexis Carrel. Carnot's portal vein injury triggered Carrel's entry into experimental vascular surgery, where his monumental achievements soon included suture repair of all types of vessels, grafts, and even transplantation of a dog's head. In 1912 he was awarded the Nobel Prize for these accomplishments.

Alexis Carrel spent his life in the laboratory, rather than in the clinical operating room, and as far as I can determine never personally repaired a portal vein. The presentation we have heard answers the question which stimulated Carrel's illustrious career. His accomplishments undergird all vascular surgery today, and I am sure that Alexis Carrel would join me in congratulating Dr. Mattox, Dr. Espada, and Dr. Beall upon their clinical solution of this problem.

DR. KENNETH L. MATTOX (Closing discussion): Dr. Stone, within the last three weeks we have had two additional injuries which arrived too late to include in the series; so now Houston has twenty-four in their total series, just as Atlanta has had. Unfortunately, both of these two patients died.

Dr. Reynolds has emphasized the difficulties of intraoperative exposure and several logistic problems. We remind you that the Fogarty balloons can occasionally be used as intravascular occluding devices in attempts to exposure.

We want to thank Dr. Dale for his historic note, and to remind him that we too are using Carrel's suture methods.

(Slide) Dr. Child has reviewed for us the effects in the primate of portal vein ligation, or occlusion, and this results in an immediate fall in blood pressure, a portal pressure which rises within thirty minutes, decrease in liver volume, and normal liver function tests soon afterwards. There is an immediate pelvic collateralization, with delayed collateralization within a month.

(Slide) Dr. Fish, from Galveston, has presented a number of techniques of repair in his review of portal vein reconstruction, both for trauma and if the portal vein has to be resected for tumor. The variety of these techniques underlines the fact that as long as accepted methods are utilized, and the portal vein is expeditiously handled, attention being placed on the other associated injuries, we can expect survival in a good number of these patients.

Hemodynamics of the Interposition Mesocaval Shunt

THEODORE DRAPANAS, M.D., JOSEPH LoCICERO, III, M.D., JAMES B. DOWLING, M.D.

Eighty interposition mesocaval shunts, using a knitted Dacron large diameter prosthesis, have been performed during the past five and one-half years. Patients were evaluated from the standpoint of protection from recurrent esophageal hemorrhage, shunt patency, encephalopathy and cumulative survival analysis. In a selected group of patients, hemodynamic measurements were also obtained in the pre, intra, and postoperative periods. These included measurements of wedged hepatic vein pressure, superior mesenteric venous blood flow, and residual superior mesenteric, hepatic sinusoidal and inferior vena cava pressures following the shunt procedure. Additionally, direct shunt flow measurements utilizing a square wave of electromagnetic flowmeter were also performed. Results indicate that the shunt patency is 95%; adequate decompression of the portal system was accomplished; recurrent variceal hemorrhage did not occur if the shunt remained patent; the incidence of encephalopathy was low (11%); and the operative mortality for the entire series was 9%. Continued perfusion of the liver was documented in 44% of patients and appears to be a function of the residual total portal resistance largely controlled by inferior vena caval pressure at the level of graft placement. Life survival analysis indicated that 72% of the patients were surviving at 5 years. It is concluded that the interposition mesocaval shunt appears to be an effective technique for the control of variceal hemorrhage, has important hemodynamic advantages and can be applied to most patients for the control of variceal hemorrhage due to portal hypertension.

IN 1968, distressed with the numerous problems related to the use of portacaval or other shunts for the relief of hemorrhage from esophageal varices due to portal hypertension, we began a prospective evaluation of the interposition mesocaval shunt which consisted of a large diameter Dacron graft interposed between the superior mesenteric vein and the vena cava. Our initial results with this form of shunt in 25 patients were reported in early 1972³ and we concluded that synthetic grafts, when placed between the superior mesenteric vein and the

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vena cava for the relief of portal hypertension, were extremely effective in protecting against recurrent hemorrhage, were easily performed, had a low operative mortality, remained patent and were accompanied with an extremely low incidence of hepatic encephalopathy. It was further suggested that a portion of portal flow to the liver could be maintained by this technique, in contrast to the total diversion of flow noted in the standard portacaval shunts.

Since our initial report, 55 additional patients have been offered this procedure. The present report constitutes our total experience to date with 80 such patients with particular emphasis on flow hemodynamics and cumulative life survival analysis.

Patient Selection

In Figure 1 is shown the classification of these 80 patients according to the criteria of Child, grouping the patients into Group A (excellent risk), Group B (moderate risk) and Group C (poor risk). The majority of patients (91%) were in the moderate and poor risk category and only 8% of the patients were excellent risks.

There were 52 men and 28 women with a median age of 46 years. The youngest patient was 21 years of age and the oldest was 69 years of age. All patients were admitted to the hospital because of the presence or history of acute variceal hemorrhage. No prophylactic shunts were performed in any patient who had never bled, despite the presence of varices.

Our initial management continues to be that of control of acute hemorrhage by Blakemore-Sengstaaken tube, restoration of blood volume, correction of metabolic al-

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1974, Boca Raton, Florida.

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Mesocaval "H" Shunt

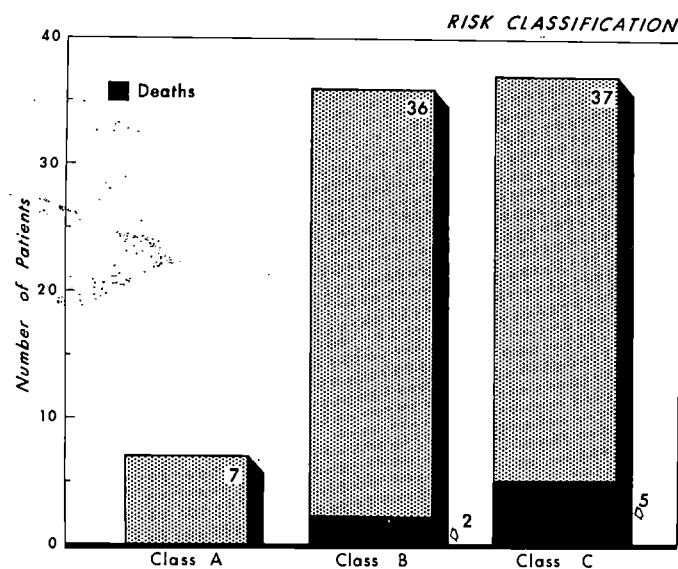


FIG. 1. Total patients in present series. Classification according to the criteria of Child.

terations, control of ascites and maximum improvement of hepatic function and nutrition. Such an elective preoperative course and evaluation was possible in 66 patients, however, in 14 patients the shunt was performed as an emergency or semi-emergency procedure early in the patient's hospital course because of continuing or recurrent hemorrhage despite the use of esophageal balloon tamponade. Thus, in 82% of the patients, the shunt was performed as an elective procedure, a factor which we believe most important in our low operative mortality and satisfactory results.

We continue to believe that the acutely bleeding cirrhotic patient with massive ascites, hypoalbuminemia, poor nutrition, and marked derangement of liver function with hepatic coma is not a candidate for emergency portacaval shunt and we do not perform a shunt under any circumstances in the latter type of patient. This approach is generally accepted by most authors in this field with the exception of Orloff and his associates¹³ who continue to routinely use emergency portacaval shunts in all patients, albeit with a very high operative mortality in the poor risk group.

We have emphasized the correction of metabolic and biochemical abnormalities including hypokalemic alkalosis and secondary hyperaldosteronism which we have encountered in over two-thirds of our patients. With potassium ion replacement and the use of spironolactone to control hypokalemia and metabolic alkalosis, along with massive infusions of salt-poor albumin to restore oncotic pressure and to aid in the control of ascites, we have been able to markedly improve the condition of

such patients, including the control of encephalopathy when present preoperatively.

Figure 1 also shows the operative mortality in this group of patients. It is predictably higher in the poor risk patient. We have had no deaths in the class A, good risk patient group to date. The overall operative mortality in the entire series was 7 patients (9%) and this has remained essentially unchanged since our initial report.

Method

Our operative technique has been previously described^{3,4} but important additional details gleaned from our larger experience are herewith presented. Most important of these relates to the *diameter* of the graft. In both experimental and clinical studies it has been definitely shown that synthetic grafts of small diameter will uniformly occlude in the immediate postoperative period. This is undoubtedly related to turbulence which, when combined with lower flows and pressures in the venous system along with the development of a thick neo-intima, will result in too small a channel in the graft to maintain flow. It has been brought to our attention that a number of surgeons during the past few years have interposed a small diameter graft (8-10mm in size) based on the erroneous concept that this will diminish shunt flow significantly in order to maintain portal perfusion and decrease the incidence of encephalopathy. In our experience such grafts are doomed to failure and we caution against their use. Furthermore, as will be subsequently detailed in our hemodynamic measurements, flow through a large diameter (18-20 mm) graft is dependent on a variety of more important factors.

Extreme care must be taken in the approach to and the dissection of the superior mesenteric vein, lest injury to the main vessel or one of its branches occur, resulting in massive hemorrhage from this high pressure system. Our approach to the superior mesenteric vein is initially directed at the root of the transverse mesocolon where the main trunk of the superior mesenteric vein crosses the fourth portion of the duodenum, just distal to the middle colic branch take-off. An important landmark here is the third position of the duodenum as it crosses beneath the superior mesenteric vein and we have found that by initially mobilizing this portion of the duodenum, the vein can be approached laterally and if necessary adequate control of bleeding can be obtained by compression of the mesenteric vein between the index finger and thumb.

We occasionally find during the dissection of the anterior surface of the retroperitoneal vena cava that it is covered by a thick, edematous layer of fibro-areolar tissue containing numerous venous collaterals. We do not hesitate to use the electrocautery freely in coagulating even the tiniest of venous collaterals and lymphatic channels in

TABLE 1. Hemodynamic Studies in Patients undergoing interposition mesocaval shunt obtained intra-operatively.*

	Pre-shunt	Post-shunt	% Change
Superior mesenteric vein pressure (mm H ₂ O)	342 ± 56	168 ± 22	↓ 51% P <0.001
Inferior vena cava pressure (mm H ₂ O)	127 ± 46	165 ± 22	↑ 30% P <0.01
Superior mesenteric vein flow (ml/min)	258 ± 42	293** ± 159	↑ 14% P >0.05

*Post-shunt flow obtained directly on graft. Pressure change in the inferior vena cava and the superior mesenteric vein were significant by Student's test. Shunt flow was not significantly different from flow in the superior mesenteric vein prior to shunt.

**Shunt Flow Measured in 4 Patients

this area for we have found that this markedly reduces operative blood loss and postoperative ascites.

We continue to prefer the large diameter (18 mm) knitted Dacron graft but have recently changed to the Weaveknit® type prosthesis which is softer and easier to suture in place. The operative time for the procedure averages 2 hours or less and rarely is more than 1 unit of blood needed for the entire procedure.

Intra-operative Hemodynamics

Intra-operative portal pressure measurements were obtained in every patient in this series before and after the mesocaval shunt (Table 1). A satisfactory reduction of portal pressure as measured through the superior mesenteric vein was noted in every patient, with a mean reduction of 51 percent. As previously pointed out, the reduction in portal pressure obtained by this technique was not as dramatic as that previously noted by ourselves and by others following a standard end-to-side portacaval shunt. The mean post-shunt portal pressure in this series was 168 mm of water and this initially caused concern. However, simultaneous measurements of inferior vena cava pressure after the completion of the shunt revealed a 30% rise to a mean of 165 mm H₂O. This caval pressure was practically identical to the mean residual portal pressure after the shunt and confirmed our thesis that the resulting caval pressure (out-flow pressure) was the controlling factor responsible for the residual pressure in the portal system. It is further evident from these pressure measurements that there was very low resistance across the shunt or a mean shunt pressure gradient from the superior mesenteric vein to the inferior vena cava of only 3 mm of water. We believe that it is this low resistance across the shunt which may also be responsible for the high rate of shunt patency encountered in this series. These residual portal vein pressures are in the same order of magnitude as those obtained by Linton and his associates following a standard splenorenal shunt⁸ and by Bismuth and his associates after splenorenal anastomosis

or after a partial direct portosystemic shunt by "small stoma" side-to-side portacaval anastomosis.²

Of further interest in these measurements is the value of flow through the anastomosis obtained by a non-cannulating square wave electromagnetic flowmeter with a probe placed directly on the shunt. In these patients a mean shunt flow of 293 ml/min was encountered with a range of 134 ml/min to 452 ml/min. When compared to superior mesenteric vein flow obtained prior to the shunt by the flowmeter in these same patients it is noted that there was only a minimal rise in flow through the graft from 258 ml/min to 293 ml/min (Table 1). This 14% increase in flow was not significant and indicates that almost all of shunt flow was derived from the superior mesenteric vein. Based on portal flow measurements previously reported by us,¹⁷ McDermott,¹⁰ Warren²³ and Moreno and their associates^{11,12} we conclude that this shunt flow represented at best no more than 50% of total portal blood flow. It can be further concluded that the shunt was obviously draining most, if not all, of the superior mesenteric vein flow and that no significant reversal of portal flow was occurring through the shunt inasmuch as direct measurement of shunt flow revealed it to be almost identical to superior mesenteric venous flow.

These hemodynamic studies confirm our earlier conclusion which was derived from angiographic studies, that the interposition mesocaval shunt was not necessarily a totally diverting shunt and that perfusion of the liver through the main portal vein was probably occurring in a significant proportion of patients, particularly in those in whom hepatic sinusoidal resistance was sufficiently low to permit this.

In Figure 2 is the pressure tracing obtained in one of our patients at the inferior vena cava before and after the shunt. The clear and distinct rise in caval pressure is noted as is the suggested pulsatile nature of the pressure in the inferior vena cava after the shunt. The latter observation appears to confirm the observation by others, that

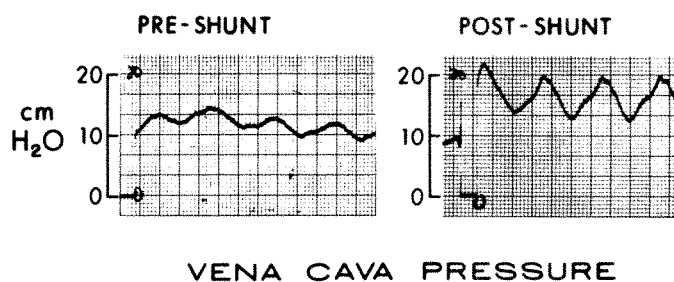
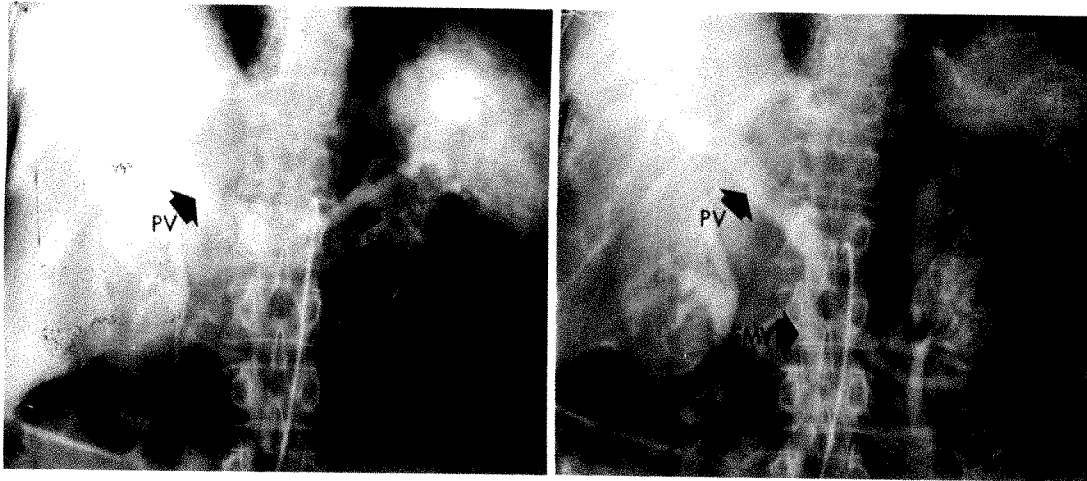


FIG. 2. Measurement of inferior vena caval pressure at level of interposition shunt, immediately prior to and after formation of the shunt. Mean caval pressure rises from 12 cm of water to 16 cm of water in this patient. The almost pulsatile nature of the caval pressure is also demonstrated.



FIGS. 3A and B. Visualization of portal venous system in patients with portal hypertension by selective celiac (A, left) and superior mesenteric (B, right) angiography. The venous phase of the contrast medium filling the splenic and portal veins is shown in A. The superior mesenteric vein and its branches are shown in B.

arteriovenous shunts may exist in the submucosa of the intestine in patients with portal hypertension and that these may play a role in the hyperdynamic cardiovascular status often encountered.

Angiographic Studies

Preoperative angiographic evaluation of the portal system by selective visceral arteriography was performed in most patients when their general condition permitted this. This information was deemed important not only to delineate the patency of the portal venous system and its major branches but also to determine indirectly the status of portal perfusion of the liver. An example of the type of

information which can be obtained in the average patient is shown in Figs. 3A and B.

Similarly, hepatic vein wedged pressures were obtained by retrograde inferior vena cava and hepatic vein cannulation in the majority of patients in an attempt to correlate preoperative wedged hepatic vein pressure to the direct intraoperative measurement of portal vein pressure. In 35 patients the preoperative hepatic vein wedged pressure of 329 mm of water compared most favorably to a mean intraoperative portal pressure of 342 mm/H₂O through the superior mesenteric vein. The difference between these measurements of 13 mm/H₂O was not statistically significant and we therefore can infer from these studies that measurement of hepatic vein wedged pressure gives an accurate assessment of mean portal pressure.

Figure 4 depicts a retrograde hepatic vein wedge injection of contrast medium and filling of hepatic vein radicals. There was rapid clearing of the contrast material indicating good portal flow through the liver in this same patient preoperatively.

Angiographic demonstration of shunt hemodynamics was also obtained in 45 patients at varying intervals following the shunt, up to 5 years postoperatively. The simplest technique to determine graft patency involves retrograde catheterization of the shunt *via* the femoral vein and the vena cava (Fig. 5B). However, we continue to prefer selective celiac and superior mesenteric arterial angiography which also permits an accurate assessment of the arterial and venous flow dynamics in such patients. This is depicted in Fig. 5A and visualization of the shunt with rapid emptying into the inferior vena cava can be readily appreciated following injection of a 50 cc bolus of contrast medium into the superior mesenteric artery and following the egress of the dye with multiple films obtained with a rapid change cassette over a 15-20 second period.

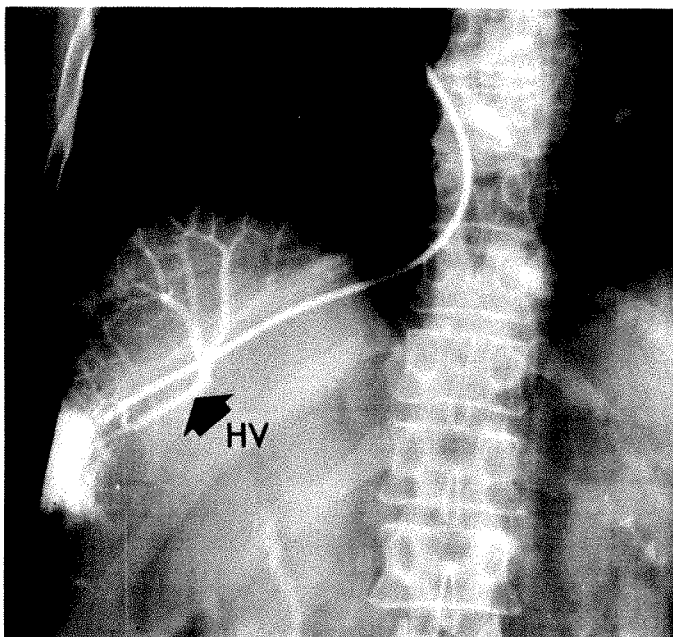
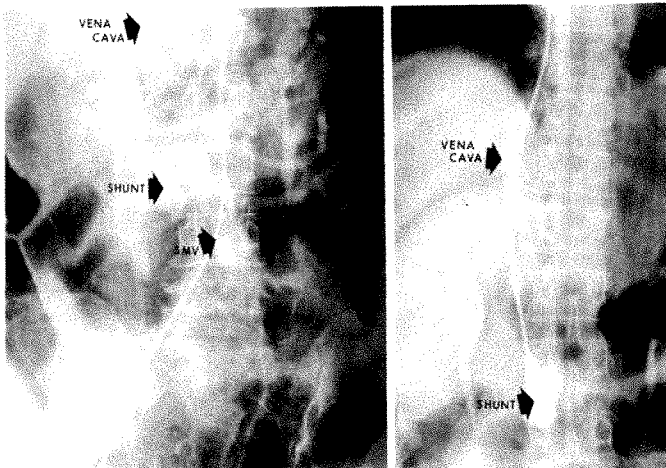


FIG. 4. Technique of hepatic vein wedge pressure measurements and injection of contrast medium to determine magnitude and direction of hepatic venous flow in same patient.



FIGS. 5A and B. Patency of the interposition graft by selective superior mesenteric injection (venous phase) is shown (A) (left). Rapid egress of contrast medium into the vena cava occurs and within two seconds all dye has left the shunt. (B right) The shunt is also visualized by retrograde cannulation via the inferior vena cava.

In Fig. 6 is shown, in the same patient as Figs. 5A and B, filling of the portal vein obtained by injection of contrast medium via the celiac axis. This flow does not appear to be static in the portal vein for the "blush" of the contrast material can be seen in the hepatic parenchyma and there is rapid emptying of this contrast material

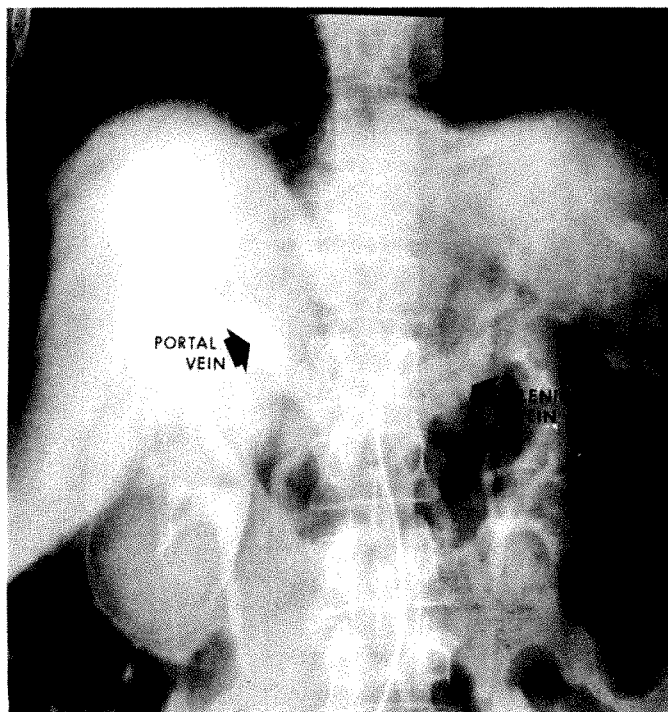


FIG. 6. Demonstration of continued hepatic perfusion via portal vein in the same patient obtained by selective celiac injection (venous phase). Rapid egress of contrast medium into the portal vein and liver is shown and the "blush" of contrast medium within the liver confirms hepatic portal perfusion.

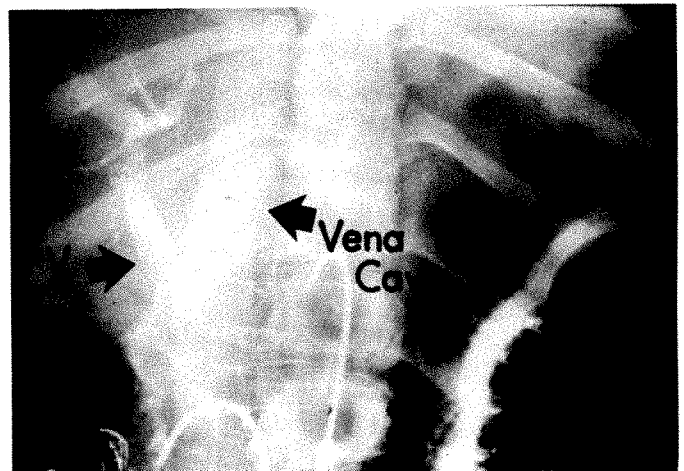


FIG. 7. Simultaneous demonstration of shunt patency with egress of dye in inferior vena cava and portal perfusion via the portal vein is shown from another patient. Two injection catheters were used in this patient and a bolus of contrast medium was injected simultaneously into the celiac axis and the superior mesenteric artery.

without further visualization of the shunt. In this particular patient it can therefore be assumed that the bulk of shunt flow was from the superior mesenteric vein while the bulk of splenic and portal flow was continuing to perfuse the liver.

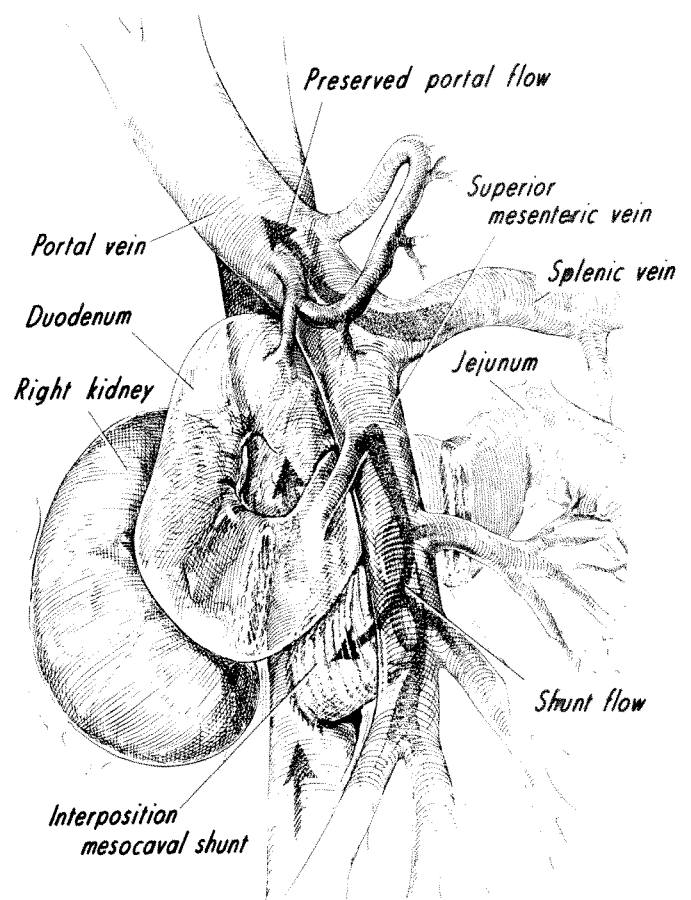


FIG. 8. Concept of partition of flow of the portal system following interposition mesocaval shunt.

TABLE 2. Incidence of Encephalopathy.

	Total Survivors	Encephalopathy		
		Mild	Moderate	Severe
Class A	7	0	0	0
Class B	34	2	0	0
Class C	32	4	2	1

Another example of continued perfusion of the liver is shown from another patient (Fig. 7). In this patient simultaneous injection of contrast medium through the celiac axis and the superior mesenteric artery reveals rapid filling of the cava *via* the shunt and also rapid filling of the portal vein and the intra-hepatic portal radicals, again indicating continued perfusion of the liver. We have been able to demonstrate hepatic portal perfusion in 20 of the 45 patients (44%) studied by this technique.

Figure 8 depicts our concept of portal flow redistribution in these patients following a successful interposition mesocaval shunt based on angiographic and flow studies. Hepatic perfusion from the portal vein is maintained from the spleen and pancreas while the superior mesenteric venous flow is diverted through the shunt. Nevertheless, what proportion of total preshunt flow this represents cannot be accurately stated for direct portal flow measurements were not obtained in all of the patients for we did not feel justified in performing the additional surgery required to dissect out the main portal vein sufficiently to place a flow probe on it except in unusual circumstances.

Shunt Patency

Of the 45 patients studied by angiographic techniques to determine shunt patency, all of the grafts except two have remained patent. In one of the patients with an occluded graft who was subsequently re-explored it was discovered that the surgeon who performed the procedure used too small a graft (8 mm in diameter). This patient was re-admitted with hemorrhage and an effort was made to insert a larger graft. However, the patient's liver function was not sufficiently good to survive the re-operation and the repeated hemorrhage and he succumbed to liver failure. The second patient in whom an occluded graft was found was re-admitted 6 months post-operatively with recurrent variceal hemorrhage. After control of the hemorrhage with a Blakemore-Sengstaaken tube, re-exploration revealed kinking of the graft, possibly due to excess length. Because of technical difficulties a new graft could not be inserted in the same location and a standard end-to-side portacaval shunt was performed. The patient had an unremarkable postoperative course and at present continues to do well one year following his second procedure. All other grafts studied to date have remained patent and our longest followup is 67 months.

Additionally, we have been able to evaluate shunt patency in 11 patients who have succumbed to their liver disease during the followup period. In 10 of the latter grafts there was complete patency with a smooth, glistening, pseudo-intima on the inner surface of the graft. One of these deaths, which occurred 3 weeks after the operative procedure, was a patient in whom a febrile course was encountered. At autopsy the graft was found to be infected and occluded. This patient, encountered early in our series, also had a gastrotomy and transgastric ligation of the varices performed at the initial operation and we suspect that contamination of the peritoneal cavity and the graft was responsible for the sepsis. We do not feel that it is necessary to ligate varices if a shunt can be accomplished and now prefer to control hemorrhage even in the acute bleeder by the continued use of the Blakemore-Sengstaaken tube if necessary throughout the operative procedure.

Our total experience with those patients studied either angiographically or at autopsy indicates that 3 out of 56 grafts thus studied have occluded, for a patency rate of 95% for the entire group. We are now in the process of evaluating the remaining patients but graft patency may be inferred for there have been no further episodes of hemorrhage in these patients in long-term followup.

Encephalopathy

The incidence of encephalopathy encountered in our series of 80 patients is depicted in Table 2. Encephalopathy of some degree was encountered in nine

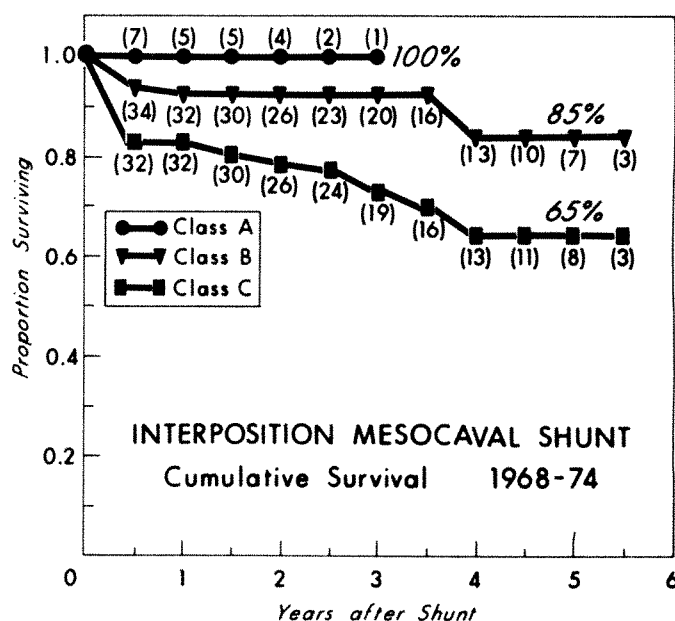


FIG. 9. Cumulative life survival table—80 patients with interposition mesocaval shunt, according to preoperative risk classification.

patients or a rate of 11 per cent. It should be noted however that many of these patients had encephalopathy preoperatively and it is difficult, if not impossible to determine what role the interposition mesocaval shunt played in producing encephalopathy in this small group of patients. This incidence of encephalopathy compared favorably to that obtained following splenorenal shunt by Grace, *et al.*,⁶ Barnes, *et al.*,¹ Bismuth, *et al.*,² Linton,⁸ and McDermott.¹⁰

Cumulative Survival

Our earlier impressions that these patients were doing very well in the followup period are confirmed by the long-term followup in the group of 80 patients. Figure 9 depicts the cumulative 5-year survival curve, calculated by the actuarial method of analysis. A separate curve is shown for the A, B and C risk groups. Of interest is the fact that there has been no operative mortality or followup mortality in the 7 patients in the good risk group. Nor have we encountered any encephalopathy in this group. All patients have returned to work and appear to be leading a normal life. However, the followup in this group of patients is not as long as in the intermediate or poor risk groups for we began applying the interposition mesocaval shunt to the A-risk patients only recently after we had become convinced of the efficacy of this procedure in the poorer risk patient. In the 5 year followup to date there is an 85% cumulative survival in the 36 patients who were in the intermediate risk (class B) category and 65% in the 37 patients in the poor risk (class C) category. The cumulative survival derived for the entire group is depicted in Fig. 10 as an overall 72% cumulative 5-year survival.

It appears clear from these survival curves that our survival experience is better than that reported by many investigators following standard, elective portosystemic shunts,^{1,6,7,10,15} except possibly for the recent reports by Lord,⁹ Bismuth² and that of Stipa and associates^{20,21} who had survival rates almost identical to ours. However, it must also be noted that 60% of the shunts performed by Bismuth, *et al.* were standard splenorenal shunts and that all of the 53 patients operated upon by Stipa and his associates had an interposition mesocaval shunt.

Discussion

Based on the observed hemodynamic changes we have derived an electrical analogue which fits well with the intraoperative studies obtained in our patients. In Fig. 11A are shown pressure and flow measurements obtained from a patient before the performance of a side-to-side portacaval shunt. By direct measurement of portal vein flow, hepatic arterial flow and wedged sinusoidal pressure, total intrahepatic sinusoidal resistance can be calculated as shown. As expected, following side-to-side por-

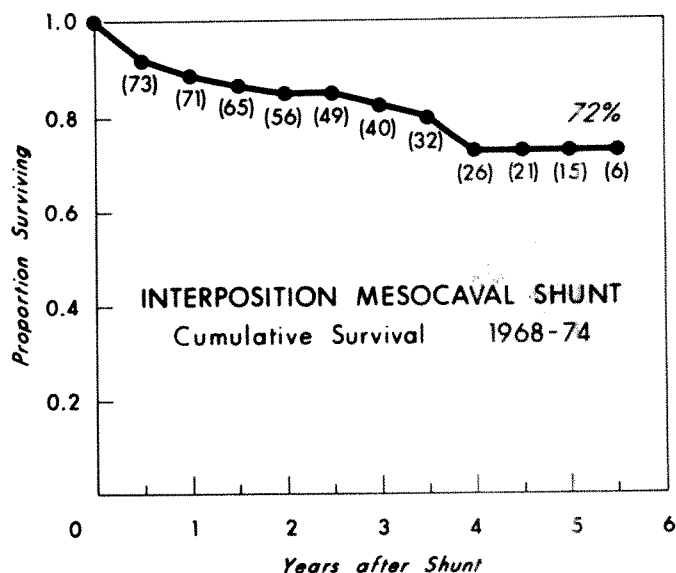


FIG. 10. Cumulative life survival analysis of entire group of patients.

tacaval shunt, a marked drop in portal pressure to 50 mm of water resulted in almost complete diversion of portal flow (Fig. 11B). Because sinusoidal resistance remains fixed due to the pathological changes within the liver, it is not surprising that in many of these patients a side-to-side portacaval shunt results in total or near total deprivation of portal flow as suggested by Warren and his associates.^{16,23,24} On the other hand, following interposition mesocaval shunt (Fig. 11C), it can be seen that a higher residual pressure in the portal system remains following the shunt and that in this patient only 50% of total portal flow was diverted from the liver. Salam and his associates¹⁶ have also noted the same phenomenon after a splenorenal shunt and attributed it to the inability of the left renal vein to accommodate the increased flow without an elevation of pressure. Our studies would seem to indicate that the flow through the interposition mesocaval shunt is not a function of the large graft diameter for there was only a 3 mm pressure gradient across the shunt, but rather a function of the outflow pressure determined by the vena cava capacitance.

Numerous investigators have recently shown a lack of

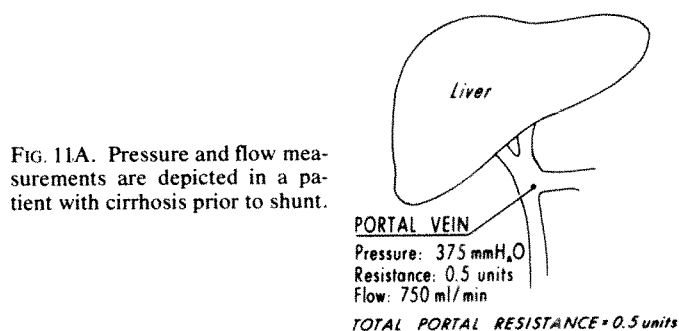
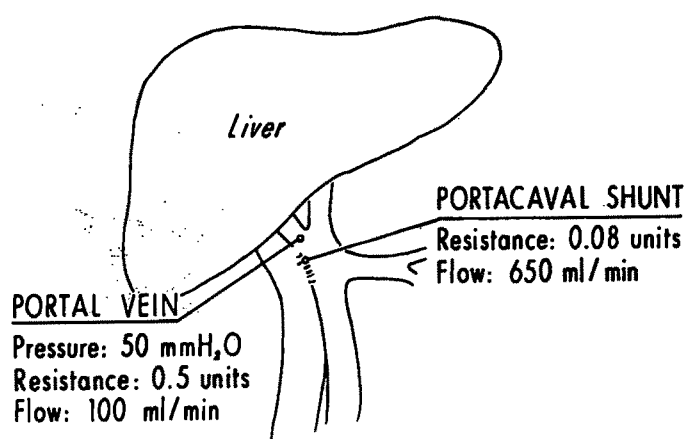


FIG. 11A. Pressure and flow measurements are depicted in a patient with cirrhosis prior to shunt.



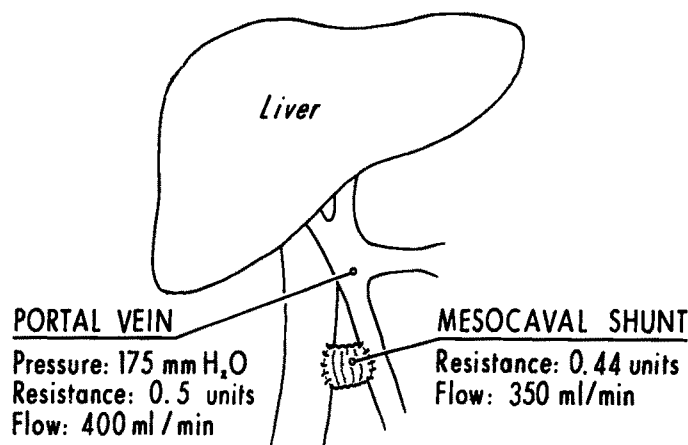
TOTAL PORTAL RESISTANCE = 0.07 units

FIG. 11B. Measurements obtained following standard side-to-side portacaval shunt.

correlation between the magnitude of portal pressure before portacaval anastomosis and the volume of portal flow. Moreno and his associates,¹¹ in studying 85 patients with cirrhosis, found an average portal flow of 6.5 ml/min/kg, measured by the square wave electromagnetic flowmeter. They concluded that the portal flow correlated poorly with portal pressure for some of the highest portal pressures are encountered in patients with the highest flows and *vice versa*. They also noted that portal flows ranged from static flow with only a slight to and fro motion during respiration to as high as 25 ml/min/kg, the latter figure well within the range of total portal blood flow encountered in normal subjects. If we apply these mean portal flow measurements to our patients following interposition mesocaval shunt we conclude that approximately 50% of total portal flow is diverted through the shunt. We can further conclude that shunt flow essentially represents superior mesenteric venous flow. On the other hand, it is also likely in those patients with balanced or stagnant portal flow resulting from very high sinusoidal resistance that total portal diversion might occur even at the flow rates measured through the shunt.

In a recent report by Moreno, *et al.*,¹² it was further concluded that there was no analytical or clinical relationship between changes in pressures on the hepatic end of the occluded portal vein (hepatic occluded portal pressure) and preshunt portal flow, nor could any correlation be found between the occluded portal pressures and postoperative survival. Similar conclusions have been reached by Smith¹⁸ and by Orloff and his associates.¹³

Maintenance of portal perfusion of the liver following interposition mesocaval shunt measured by angiographic technique has also been confirmed by Thompson and Read,²² by Lord and his associates,⁹ and by Stipa.²¹



TOTAL PORTAL RESISTANCE = 0.23 units

FIG. 11C. Measurements obtained from another patient following interposition mesocaval shunt. It will be noted that total portal resistance following interposition mesocaval shunt (0.23 units) is considerably higher than following side-to-side portacaval shunt (0.07 units) but lower than the patient prior to the performance of the shunt (0.05 units).

Reichle¹⁴ has measured portal blood flow in a series of patients pre- and postoperatively using a unique quantitative technique of infusing droplets of lipiodol directly into the portal vein *via* the cannulated umbilical vein. He demonstrated that following interposition mesocaval shunt in a small number of patients, approximately half of the portal flow continued to perfuse the liver. Mean pre-shunt portal flow was 529 ml/min and this was reduced to 246 ml/min postshunt. By extrapolation, the average mesocaval shunt flow in his patients was 283 ml/min which agrees closely with our average measured shunt flows of 293 ml/min. Interestingly, the reduction of portal flow following interposition mesocaval shunt was of the same magnitude as the reduction in portal flow measured by him in a parallel series of patients who had undergone a distal splenorenal shunt according to the technique of Warren.²⁴

In a significant experimental study in animals reported by Starzl and his associates¹⁹ he found that perfusion of the liver by pancreatic venous blood flow was important in maintaining the integrity of the liver. Starzl has postulated that this important substance may be insulin and that it is important to preserve this portion of pancreatic blood flow to the liver. This evidence lends strong support to the need for maintenance of a portion of portal flow, particularly from the upper abdominal viscera as has been demonstrated in our patients following interposition mesocaval shunt.

Using our hemodynamic studies we have developed an electrical analogue of the portal system (Fig. 12). In this analogue we have shown in electrical terms the measurements derived in a patient with portal hypertension prior to a shunt; following a side-to-side portacaval shunt; and following an interposition mesocaval shunt. It

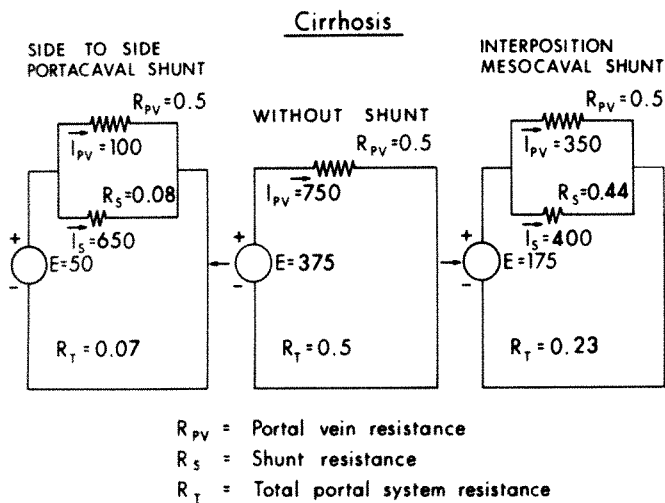


FIG. 12. Electrical analogue of portal system based on pressure and flow measurements in this series of patients.

can be seen that there is a good correlation between the predicted flows and pressures in the theoretical analogue and the actual measurements obtained in Fig. 11. We are now applying this analogue to intraoperative hemodynamic studies in order to evolve a better understanding of portal hemodynamics in cirrhosis.

Finally, it should be stated the results we have encountered in this series to date should not necessarily be attributed entirely to the type of shunt being performed. We feel that equally as important is the careful management of the patient preoperatively, control of hemorrhage by balloon tamponade, restoration of metabolic imbalances, potassium repletion and the use of aldosterone antagonists. Similarly, careful postoperative care is required in such patients including the administration of albumin, monitoring of serum electrolytes, particularly potassium, and the maintenance of nutrition. With better preoperative preparation of the patient and improved postoperative care in addition to a simpler operative technique which preserves at least a significant portal blood flow we feel that the whole outlook on the surgical management of portal hypertension has changed.

Conclusions

We conclude from this study of 80 patients with interposition mesocaval shunt that the shunt is readily performed, carries a low operative mortality (8%), a low incidence of encephalopathy (11%) and that it can be applied to most, if not all patients with portal hypertension due to cirrhosis of the liver. In 44% of the patients continued perfusion of the liver was demonstrated by angiographic techniques. Shunt flow was measured at 293 ml/min, a figure which is approximately 50% that of calculated mean portal flow in these patients.

Cumulative life survival tables indicate an overall 75% 5-year survival in the entire group. It was 100%, 85% and

65% for the good, intermediate and poor risk patients, respectively.

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DISCUSSION

DR. JERE W. LORD, JR. (New York, New York): About two and a half years ago I had the privilege of discussing the first presentation of Dr. Drapanas. At that time he had 25 patients, and my associates and I also had 25 patients. At the present time he has recorded 80, and we have about 40.

We all agree on all but one point: first, he has proven that the patency of these shunts is of a very high order. This was a worry that concerned us in the beginning. When we first began to use them, we were encouraged by Dr. Foster's stimulating paper some years ago which showed that the prostheses remain patent in experimental animals and also in one human between the portal vein and the vena cava.

Secondly, the mortality rate has been acceptable; lower, perhaps, than the mortality rate of other types of shunts.

Thirdly, I think the timing of the procedure, which he did not have a chance to bring out in the presentation, is important. It is better to control the acute hemorrhage by a Blakemore-Sengstaken tube, or by some other method, and operate on these patients when they are brought into the best possible in all patients, and some have to be operated as an emergency. With this we agree.

Our only point of disagreement is the explanation of the relatively low flow rate through these shunts. He believes that the relatively small fall in pressure, 168 mm of saline in his patients, 165 on the average in ours, of the portal pressure is that the pressure in the vena cava is high enough to lessen the gradient of pressure and lower the flow. I believe another reason may be suitable, and that is that the prosthesis is about 18–20 mm in diameter, the vena cava is of equal or a little larger but that the limiting factor is the superior mesenteric vein, which in our measurements has been between 9 and 11 mm in diameter. This is of about the same order as the splenic vein; and whereas this procedure can be accomplished much more frequently than splenectomy and splenorenal shunt, our own experience with the latter procedure has been an extremely salutary one. Our followup of ten years and longer in a small series of patients operated from 1953 to 1963 showed that 67% live ten years and longer. Recently in the office I saw a patient we did 16 years ago, and one 13 years ago, and both are in excellent health. Therefore, I believe that the size of the mesenteric vein may be the limiting factor in the modest fall of the portal pressure, in contrast to the large portacaval shunt with an end-to-side or a side-to-side anastomosis.

In conclusion, I'd like to congratulate Dr. Drapanas. I believe he has shown on sound physiological and clinical bases that the interposition mesocaval shunt is an excellent one.

DR. GARDNER W. SMITH (Baltimore): I would first like to congratulate Dr. Drapanas on what is truly a superb series and superb results. Particularly impressive are his five-year survival statistics, which I don't think have been equalled in any other shunt series.

It is interesting to me that he has also presented some elegant hemodynamic data, and I think that this serves to make one point at least, and that is that even when you have good results with some form of portal-systemic shunt or other, you must explain why hemodynamically. I don't know whether that's a real requirement, or just a continued fetish.

I would like to present briefly the experience we have had at The Johns Hopkins Hospital over the past 2½ years with this same shunt; and this represents primarily the work of Drs. John Cameron, Willis Maddrey and George Zuidema. I do this to make two points, one in agreement and one, perhaps, in discussion.

First, among a very modest series, now only 19 patients, we have had very good risk patients; 16 of them or 84% were Class A or Class B. On the other side of the coin, 12 of the 19 were done either as emergency or semi-emergency shunts; so that only 37% of them were elective. The striking part about these 19 patients is that there has been only one death; or an operative mortality of 5%.

I think this is a very important point. It seems clear that in our hands, as in Dr. Drapanas', this shunt can be done with less risk than the standard portacaval shunts.

On the other hand, among these same patients there have been seven with encephalopathy, three in the acute postoperative phase and four long-term, and two of these patients have died with liver failure. That's a 37% incidence of encephalopathy. And that, indeed, is no improvement over what has been accomplished with the portacaval shunts.

I think we would conclude from this modest experience that this operation can be done more easily than a standard portacaval shunt, and with considerably less risk, and that that is its primary value. We have been unable to demonstrate a decreased incidence of encephalopathy. We have had no opportunity to compare this type of procedure with the innovative one that Dr. Warren has described, the distal splenorenal shunt, and the reason is that we simply don't see patients who are candidates. As I indicated to you, two-thirds of these patients were emergencies, and one of the elective ones had significant ascites. Thus, in 2½ years, even had we wished to compare this with the distal splenorenal shunt, we would have had only six patients who were candidates for that procedure.

DR. FREDERICK A. REICHLE (Philadelphia): The hemodynamic observations which Dr. Drapanas has reported represent an important contribution to our understanding of the hemodynamic sequelae following mesocaval decompression through a large-bore prosthetic. These data are of special importance because of the favorable clinical response of his patients to H-graft portal decompression.

Hemodynamic alterations caused by iatrogenic portosystemic shunt, superimposed on highly valuable preshunt hemodynamic patterns, are the underlying cause of the metabolic changes of clinical hepatic failure, which is the most common cause of death and morbidity after portosystemic shunt. Thus postshunt metabolic changes may be the result of qualitative or quantitative alterations in the hepatic blood supply.

The relevance of the preoperative and postoperative hemodynamic patterns to the clinical outcome after portosystemic shunt has been emphasized by Dr. Warren, and has also been reported by Dr. McDermott and others. Because of the superior results of operative treatment of patients with portal hypertension which have been reported by Dr. Drapanas, using the mesocaval H-graft, and by Dr. Warren, using the distal splenorenal shunt, we recently began a study of the hemodynamic and metabolic sequelae in randomized patients with these two operations. The method of direct portal flow determination used in this study has been reported previously, and involves the use of intraportal radiopaque water immiscible droplets to determine the flow velocity in the portal vein done together with biplane portography of the portal vein.

Using this technique, which can be done in the unanesthetized and unsedated patient, having gained access to the portal vein by a previously placed umbilical catheter, we have studied a small number of patients before and after Drapanas' shunt. These preliminary results of the differences between pre and postoperative portal blood flow at this time are very comparable to the data that Dr. Drapanas has accumulated by direct operative measurement of flow through the mesocaval H-graft. Whereas these data are highly preliminary, perhaps they are significant only inasmuch as there is a close correlation with Dr. Drapanas' data. As time goes by, such preliminary data is subject to change particularly in view of the highly variable preoperative portal hemodynamic patterns.

In addition to randomizing patients requiring elective shunt into Drapanas H-graft and Warren distal splenorenal shunt, we are currently using the H-graft as the treatment of choice in patients with variceal hemorrhage which we are unable to stop short of operation—that is, for emergency portosystemic shunt—and have been impressed by how well patients frequently come through very severe clinical straits associated with emergency portosystemic shunting.

Inasmuch as there is a 72% survival in five years, I would like to ask whether Dr. Drapanas has had an opportunity to analyze the morphology of the Dacron graft since this is a unique experience in which a prosthetic material is in the functioning venous system for a prolonged period of time. I would also like Dr. Drapanas to speculate on the cause of the increased vena caval pressure which may serve to retard the blood flow through the H-graft shunt.

DR. ROBERT B. SMITH, III (Decatur, Georgia): We have had an interest in the interposition dacron shunt at Emory, and have used both the mesocaval type described by Dr. Drapanas, and also an innovation, the mesorenal H-graft, as total shunting procedures against which we have randomized Dr. Warren's distal splenorenal shunt in a prospective, controlled series lasting now over 40 months. We have also used the interposition shunt on many occasions when it was not possible to perform the distal shunt because of the presence of persistent ascites of

the nonavailability of the splenic vein for the distal shunting procedure.

Our operative death rate and late death rate with the interposition shunt have been remarkably similar to those reported by Dr. Drapanas, although our followup is not as his.

The one major difference between the Emory experience and that of Dr. Drapanas is that our incidence of post-operative encephalopathy has been much higher with the interposition shunt. We have observed this distressing complication in 36% of our interposition shunt patients. This figure corresponds very closely with our incidence of encephalopathy in other forms of total shunts, and also that reported from other authors with total shunts.

(Slide) This illustrates the Emory experience to date with interposition shunts over the last 40 months: 45 total patients, 22 of whom fell in the randomized study; there were no operative deaths among the randomized patients and five operative deaths among the nonrandomized ones. Many of these were poor risk patients who had emergency procedures. Our late deaths are five among randomized patients, and three more among the total. Again I would point out that the encephalopathy rate with the total shunts by graft interposition is 36% in the whole group, and 32% among the 22 randomized patients.

(Slide) By comparison, this is our experience over the same period of time at Emory with the selective distal splenorenal shunt: 38 patients total, 22 of whom were in the randomized series; no deaths have occurred to date in the randomized series, and only one among nonrandomized distal shunts; late deaths were one in the randomized group, and two more in the total series. Only one patient from the entire group of selective distal shunts has developed postoperative encephalopathy. I would hasten to add that the diagnosis of encephalopathy has not been based entirely on assessment by the operating surgeons, since the majority of these patients have been carefully evaluated by a hepatologist and by a research clinician whose primary interest is in the field of protein chemistry.

In conclusion, I would like to ask Dr. Drapanas if he could describe the criteria that he employs to make the diagnosis of encephalopathy, as that might explain some of our differences.

DR. THEODORE DRAPANAS (Closing discussion): I'd like to tackle, first of all, Dr. Gardner Smith's question about when we do these shunts. We still feel that cirrhosis is a bad disease to have, and that surgery is bad for the liver. Regardless of what type of shunt is performed, it should be performed under nonemergent conditions when the patient is in optimal clinical condition.

We have recently found that a number of surgeons have reserved the mesocaval shunt for the poorer risk patients (those with acute exanguiation) massive ascites, convulsing with coma; and I am reminded of a statement often made, that when you operate on dying patients, you get deaths.

Our encephalopathy rate was 35%, in this type of patient operated upon in poor condition as an emergency.

Therefore, we spend a great deal of time in getting these patients into better condition preoperatively. We were successful in this approach with 85% of our patients for whom the operation was done electively. We do not feel, as we have commented upon in the manuscript, that an emergency shunt should be performed except in a few selected good risk patients and we don't see many of the latter in our institution.

Finally, I think it's most important to be aware of the metabolic alterations in these critically ill patients and there are many. Of great importance is the prevention of alkalosis and hypokalemia which tends to predispose to encephalopathy, with or without a shunt. We prefer to place these patients on spironolactone, an aldosterone antagonist, and also restore potassium ion deficits, which almost all of these patients have.

With good medical care we think we can control encephalopathy. The criteria that we use for the diagnosis of encephalopathy include careful history, physical examination, neurological evaluation, and, finally, arterial blood ammonia levels, which don't always correlate, as we all know well, with encephalopathy.

Now, I would like to answer Dr. Lord's and Dr. Reichle's questions by showing some additional data from our manuscript. This depicts an electrical analog of the portal system based on our flow hemodynamic studies. The important point to be made relates to R_t , (total portal system resistance) calculated from hemodynamic studies obtained for three different groups of patients, with side-to-side shunts, without shunts, and patients with interposition mesocaval shunts. In the patient with cirrhosis and portal hypertension without a shunt R_t is 0.5 units; with interposition mesocaval shunt, about half of that, 0.23 units. But look what happens to R_t with a side-to-side shunt. It is reduced even further. We think that this is what increases the diversion of flow from the liver.

We do not agree with you, Dr. Lord that it's the function of the size of the mesenteric vein. By simply occluding the vena cava distal to the shunt, thereby removing competitive flow from the legs, while studying flow through the shunt, we find that it doubles.

Perhaps, if I might answer Dr. Frank Spencer's question which he asked me three years ago when we presented our initial studies, now, with this data, I can tell you that one of the reasons we feel the flow is low is that we are shunting into an area of higher vena caval pressure, or higher capacitance in the caval system.

Finally, Dr. Sabiston, if you will permit me to borrow a page from your splendid address this morning, I would like to give a tribute to one man who has, perhaps, stimulated us more than anything else to go into these studies, and that is, of course, our erstwhile Secretary, Dr. Warren, who is being eminently fairminded and totally objective about the matter of shunts, and challenged us last year at The Homestead to look at our studies.

Results of Radical Resection for Periapillary Cancer

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This report concerns 348 pancreatoduodenectomies, including 13 total pancreatectomies. Operative mortality over 30 years was 15%, operative mortality since 1962, 10%. Precise factors influencing operability, mortality, morbidity, and long-term palliation or cure are emphasized. The necessity for making a distinction among tumors arising in the ampulla of Vater, the intrapancreatic portion of the common bile duct, and the duodenum surrounding the papilla of Vater and carcinomas arising in the head of the pancreas is the most important factor in the approach to periapillary malignant tumors. Even with this large experience, the impression of the operating surgeon at the time of resection was incorrect in 10% of the patients in whom a resection was carried out for a tumor assumed to arise in the head of the pancreas. Thus, surgeons who do not resect carcinomas arising in the head of the pancreas and who may have had less experience in this specialized field may be rejecting an even larger per cent of patients with more favorable periapillary malignant tumors. The influence of previous exploration, manipulation, and biopsy on morbidity, mortality, and survival is discussed. The significance of nodal involvement and residual tumor at the neck of the pancreas and the point of division of the common bile duct and the uncinate process is discussed. These data justify continued selective application of pancreatoduodenectomy for periapillary cancer and identify areas where further improvement can be made.

RADICAL RESECTION for periapillary tumors at the Lahey Clinic Foundation has been based on the anatomic principles advocated by Whipple in 1935.²⁸ Over the years, as a result of increasing experience, specific modifications have been adopted, including total pancreatectomy under certain circumstances.^{7,25,26} Although

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this practice has been amply justified by previous reports, some controversy still persists regarding the preferred surgical approach, particularly in the case of adenocarcinoma of the head of the pancreas.^{9,11,18,19,26,27} On the one extreme, more extensive resections, including vascular resection, have been advocated for more advanced tumors.^{1,6,8,9,17,20} However, neither the bypass procedure nor the more radical resection has been justified by results to date.^{1,6,8,9,20}

The resectability rates for malignant jaundice have varied from 8 to 30%.^{2,4,29} Although these resectability rates are relatively low, the magnitude of the surgical problem is best indicated by considering that 348 resections for periapillary cancer have been performed at one institution during the past 30 years. This report is submitted for the purpose of defining further the problems of morbidity and mortality associated with radical resection for periapillary cancer and to present survival figures based on pathologic findings, including site of tumor, type of tumor, the presence and absence of lymph node metastases, and marginal involvement.

Methods and Results

The charts of 355 patients who underwent pancreatoduodenal resections of periapillary tumors from 1942 to 1971 were reviewed. Operative deaths were defined as those deaths occurring after operation in the hospital and all those who died within 30 days after discharge from the hospital. Relative survival rates were determined after excluding operative deaths and patients with incomplete followup studies. The effect on survival rates was determined for the site of tumor, the presence of lymph node

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TABLE 1. *Patients Treated by Pancreatoduodenectomy or Total Pancreatectomy*

Site	Malignant Tumors	Benign	Total
Pancreas	150	4	154
Ampulla	112	1	113
Common bile duct	47	2	49
Duodenum	39	0	39
Total	348	7	355

metastases in the excised specimen or in the nodes biopsied during operation, and the type of tumor.

No obvious difference was found in the ages of patients when compared to the site of the tumor. The ages varied from that of a 12-year-old girl with cancer of the head of the pancreas to that of a 78-year-old man with cancer of the common bile duct. The mean age for all 348 patients was 56.3 years.

Pathologic examination of 355 surgical specimens resected because of the clinical and operative diagnosis of periampullary cancer demonstrated that 6 resections were for pancreatitis and one was for benign papillary cystadenoma. The remaining 348 resections, which form the basis of this report, were for malignant tumors. The 348 resections included 13 total pancreatectomies, 12 of which were for cancer of the head of the pancreas, and 1 for cancer of the common bile duct (Table 1).

The histologic type of tumor was adenocarcinoma in 331 (95.2%) of the 348 patients with malignant disease. The other 17 included 6 islet cell tumors, 4 carcinoids, 2 cystadenocarcinomas, 2 adenoacanthomas, 1 neurofibrosarcoma, 1 melanoma, and 1 leiomyosarcoma (Table 2).

The surgeon's conclusions regarding the site of origin of all periampullary cancers at operation were compared with the pathologist's findings. This demonstrated that 20 of the 198 cancers of the ampulla, common bile duct, and duodenum were mistaken for cancer of the pancreas. This 10% consisted of 9 cancers of the ampulla, 8 cancers of the common bile duct, and 3 cancers of the duodenum.

TABLE 3. *Operative Mortality (1962-1971)*

Site	Number of Cases	Operative Deaths	Per Cent
Pancreas	58	6	10.3
Ampulla	39	3	7.6
Common bile duct	23	4	17.4
Duodenum	19	2	10.5
Total	139	15	10.7

Determination of the 30-year operative mortality according to the site of origin of the tumor showed that there was a mortality of 21% for cancer of the common bile duct; the next highest mortality was 18% for cancer of the duodenum. The lowest mortality was 11% for cancer of the ampulla, whereas there was a 15% mortality for cancer of the pancreas. During the last 10 years, resections for common bile duct cancers continued to have a relatively high mortality of 17.4%, while the mortality for ampullary cancer resection was 7.6%. Mortality for resection of the duodenum and pancreas was reduced to 10.5 and 10.3% respectively (Table 3).

Operative mortality for the 348 resections was 52 deaths (14.9%). Hemorrhage, sepsis, cardiopulmonary problems, renal failure, and necrotizing pancreatitis were the major life-threatening complications causing 44 of the 52 deaths. Sepsis caused 9 deaths, and cardiopulmonary complications caused 7 deaths. The mortality rate for the 10 patients with renal failure was 60%, and 3 of the 4 patients with necrotizing pancreatitis died. There were 28 pancreatic leaks resulting in two deaths. Of the 23 biliary leaks one was considered a cause of death. There were four gastric leaks, none of which caused death. Other complications included hepatic failure which caused two deaths, shock of unknown cause which caused two deaths, and a fatal cerebrovascular accident (Table 4).

Since 1962 the operative mortality for 139 resections was 10.7%. Hemorrhage was again the most serious complication occurring in 13.7% with a mortality of 36.8%. Pancreatic leak occurred in 5 patients and caused one death. No

TABLE 2. *Histologic Type of Tumor*

Type of Tumor	Pancreas	Ampulla	Common Bile Duct	Duodenum	Total
Adenocarcinoma	138	109	47	37	331
Islet cell tumors	6	0	0	0	6
Carcinoid	1	2	0	1	4
Cystadenocarcinoma	2	0	0	0	2
Adenoacanthoma	1	1	0	0	2
Neurofibrosarcoma	1	0	0	0	1
Melanoma	1	0	0	0	1
Leiomyosarcoma	0	0	0	1	1
Total	150	112	47	39	348

TABLE 4. *Operative Morbidity and Mortality: 348 Resections (1942-1971)*

Major Complications	Number of Cases	Cause and Number of Deaths
Hemorrhage	41	19
Pancreatic leak	28	2
Cardiopulmonary	25	7
Biliary leak	23	1
Sepsis	23	9
Renal failure	10	6
Intestinal obstruction	6	0
Necrotizing pancreatitis	4	3
Gastric leak	4	0
Hepatic failure	4	2
Hyperglycemia	4	0
Thrombophlebitis	3	0
Cerebrovascular accident	3	1
Shock	2	2
Acute parotitis	2	0
Total	182	52 (14.9%)

deaths were attributed to any of the 16 biliary leaks. Sepsis and cardiopulmonary complications continued to be frequent and serious (Table 5).

Survival rates according to the site of tumor demonstrate that less than half (46%) of patients with pancreatic carcinoma survived one year, which is in marked contrast to the fate of patients with tumors at the other periampullary sites. A steep decline in survival occurred in patients with ampullary, common bile duct, and duodenal tumors during the second and third years although 5-year survivals of 41% and 32% were obtained respectively for duodenal and ampullary tumors, while the survival rate for common bile duct cancers was 25%. At 5 years the survival rate for cancer of the pancreas had fallen to 12.5%. Long-term survival results, up to 15 years, demonstrate a steady decline for tumors at all periampullary sites except in the case of the common bile duct, which does not show such a decline and for which a 38.4% 15-year survival rate was obtained (Table 6).

TABLE 5. *Operative Morbidity and Mortality: 139 Resections (1962-1971)*

Major Complications	Number of Cases	Number of Deaths
Hemorrhage	19	7
Biliary leaks	16	0
Cardiopulmonary	15	3
Sepsis	10	3
Pancreatic leaks	5	1
Renal failure	4	0
Necrotizing pancreatitis	2	1
Cerebrovascular accident	2	0
Gastric leaks	1	0
Hepatic failure	1	0
Acute parotitis	1	0
Total	76	15 (10.7%)

There were 87 (25%) patients with metastases to one or more lymph nodes. There was an incidence of 28% regional lymph node metastases associated with cancer of the pancreas and 28% in the case of ampullary and duodenal cancers. Lymph node metastases were found in 13% of cancers of the common bile duct.

Of the 348 resections, 261 (75%) patients had no evidence of regional lymph node metastases (Table 7A). There is only a 41.1% one-year survival rate for cancer of the head of the pancreas, whereas the one-year survivals for patients with tumors at the other sites range from 75.7 to 90.4%. Again, there is a steep decline in survival rates between the first and third years in the case of ampullary, common bile duct, and duodenal tumors. In the case of long-term survivals, a steady decline continues for both ampullary and duodenal cancers, while there is an actual improvement in survival rates for common bile cancers as already seen for all cases according to site of the tumor (Table 6). Survival rates shown in Table 7B demonstrates a marked drop after one year for ampullary, common bile duct, and duodenal cancers, resulting in only 4 patients surviving in 5 years. The results for cancer of the head of the pancreas, however, show a remarkable 60% one-year survival rate, but only 2 of 27 patients survived 5 years.

Marginal involvement was found in 18 (13%) of the 150 resected tumors of the pancreas and in 6 (12.5%) of the 47 resected tumors of the common bile duct. No marginal involvement was found in the case of duodenal or ampullary tumors. There was only one 3-year survival among those with marginal involvement, and that patient had carcinoma of the head of the pancreas.

Of the 150 patients with cancer of the head of the pancreas, 12 had tumors other than adenocarcinoma and 6 of these had islet cell cancers (Table 2). Survival rates for the 10 patients eligible for followup demonstrate relatively satisfactory results with a 5-year survival of 40% (Table 8).

Discussion

The problem of avoiding unnecessary resection for chronic pancreatitis can be a challenge to the surgeon operating on patients with obstructive jaundice. The less than 2% incidence of such resections in this series was achieved by careful evaluation of the history, physical findings, and results of investigations before operation. During exploration, particular attention was given to changes in the distal pancreas. The duct of Wirsung is dilated in 80% of the resectable tumors, and the body and tail of the pancreas are enlarged, pale, and firm.²⁷ Examination of the common bile duct and the gallbladder, which are obstructed owing to carcinoma of the head of the pancreas, will reveal a thin-walled gallbladder and bile duct with a bluish color. In the majority of cases, a diagnosis was made without biopsy of lymph nodes or of the primary lesion. In the cases where doubt still existed regarding the nature of the lesion, the next step was peripancreatic and common

TABLE 6. *Relative Survival Rates According to Site of Tumor*

Site	1-Yr Survivals	3-Yr Survivals	5-Yr Survivals	10-Yr Survivals	15-Yr Survivals
	1942-1971	1942-1969	1942-1967	1942-1962	1942-1957
Pancreas	46.6% (56/120)*	15.7% (18/114)	12.5% (13/104)	8.6% (7/81)	3.5% (2/56)
Ampulla	83.2% (79/ 95)	44.4% (40/ 90)	32.0% (26/ 81)	35.3% (18/51)	23.6% (9/38)
Common bile duct	76.3% (29/ 38)	32.3% (11/ 34)	25.0% (8/ 32)	28.5% (6/21)	38.4% (5/13)
Duodenum	93.5% (29/ 31)	45.1% (14/ 31)	41.3% (12/ 29)	25.0% (4/16)	18.1% (2/11)

*Numbers in parentheses indicate survivors and patients eligible for followup.

bile duct node biopsy. If diagnosis was still in doubt, choledochostomy and, if indicated, duodenotomy were carried out to obtain tissue from the distal common bile duct and ampulla.²⁵ When indicated biopsy of the head of the pancreas was undertaken by making a rectangular-shaped incision over the tumor and then gently scooping out tissue with a bone curet. This method of biopsy has been found satisfactory and is associated with no complications.

It is important to bear in mind that cancers other than adenocarcinoma can occur in the periampullary area and that resection for such cancers results in relatively satisfactory survival rates (Table 7). Twelve such tumors occurred among the 150 cases of cancer of the head of the pancreas in this series (Table 2).

The difficulty in determining the exact site of the tumor during surgery is demonstrated by the pathologic reports of the resected specimens. The reports revealed that, at the time of operation, 10% of periampullary tumors arising in the ampulla, common bile duct, and duodenum was mistaken for tumors of the head of the pancreas. The importance of this figure is obvious in circumstances when only bypass procedures are carried out for cancers of the head of the pancreas, and it is especially important when one considers the overall national figures involving thousands of patients annually.^{5,12} These findings demonstrate the difficulty of interpreting the results of the bypass operation for resectable tumors which were considered cancers of the head of the pancreas during exploration.⁹ Furthermore, this figure of 10% for these tumors with a relatively favorable prognosis occurred at a center specializing in this type of disease.

The operative mortality in this series, particularly during

the 10 years from 1962 to 1971, corresponds fairly well to that found by other authors.^{2,10,15,16,21-24} Measures to reduce operative morbidity and mortality include careful preoperative evaluation with particular attention to blood volume, hypoproteinemia, prothrombin determinations, and electrolyte balance. The correction of hypovolemia has been shown to be a major factor in reducing operative mortality.²⁹ As operative experience has been gained over the years, there has been a substantial reduction in the number of anastomotic leaks (Tables 3 and 4). In this study, there were 5 pancreaticojejunostomy leaks after 1972 as opposed to 23 before 1962. Furthermore, the mortality associated with pancreatic leaks can be reduced by proper use of sump drains. The lower mortality rate during the past decade was mainly the result of absence of death from renal failure (Tables 3 and 4). Hemorrhage, sepsis, and cardiopulmonary complications are still the principal causes of morbidity and mortality. A further significant reduction in the morbidity and mortality rates associated with this operation will be achieved only by the prevention of these problems and improved methods of management.^{15,16,22} As a result of experience at this clinic, it is suggested that management of postoperative hemorrhage during the initial phases, whether intraperitoneal or gastrointestinal, should be based on conservative principles. Reexploration should only be considered in patients whose condition continues to deteriorate despite vigorous treatment, which may involve transfusion of 10 to 12 liters of blood.

Since 6 deaths were directly related to the residual pancreas (4 were due to acute necrotizing pancreatitis and 2 were due to pancreaticojejunostomy leak) total pancreatectomy should be considered in those patients in

TABLE 7 A. *Relative Survival Rates According to Site of Tumor without Lymph Node Metastasis*

Site	1-Yr Survivals	3-Yr Survivals	5-Yr Survivals	10-Yr Survivals	15-Yr Survivals
	1942-1971	1942-1969	1942-1967	1942-1962	1942-1957
Pancreas	41.0% (35/85)*	21.6% (18/83)	16.8% (13/77)	10.9% (7/64)	4.3% (2/46)
Ampulla	88.0% (59/67)	49.2% (32/65)	40.0% (24/60)	35.3% (18/51)	23.6% (9/38)
Common bile duct	75.7% (25/33)	35.4% (11/31)	27.5% (8/29)	33.3% (6/18)	41.6% (5/12)
Duodenum	90.4% (19/21)	52.3% (11/21)	50.0% (10/20)	33.3% (4/12)	18.1% (2/11)

*Numbers in parentheses indicate survivors and patients eligible for followup.

TABLE 7 B. *Relative Survival Rates According to Site of Tumor with Lymph Node Metastasis*

Site	1-Yr Survivals	3-Yr Survivals	5-Yr Survivals	10-Yr Survivals	15-Yr Survivals
	1942-1971	1969-1972	1942-1967	1942-1962	1942-1957
Pancreas	60.0% (21/35)	6.4% (2/31)	7.4% (2/27)	5.8% (1/17)	
Ampulla	71.4% (20/28)	28.6% (8/28)	9.5% (2/21)		
Common bile duct	80.0% (4/5)				
Duodenum	100.0% (10/10)	30.0% (3/10)	22.2% (2/9)		

*Numbers in parentheses indicate survivors and patients eligible for followup.

whom there is difficulty in making the pancreaticojejunostomy anastomosis.

In this study, marginal involvement was found in 13% of the common bile duct and pancreatic tumors and may well represent an advanced stage of tumor growth. As a result of finding marginal involvement in 4 of their 10 patients, Hicks and Brooks¹¹ have advocated total pancreatectomy for cancer of the head of the pancreas. However, Smith²³ has noted that recurrence in the residual pancreas is not one of the major problems following resection for this disease. The Whipple type of operation continues to be the procedure of choice at the Lahey Clinic for cancer of the head of the pancreas.

Analysis of survival rates in this series confirms the relatively favorable prognosis for duodenal, ampullary, and common bile duct cancer, particularly when there is no associated lymph node metastases. Although no resections were performed when lymph node metastases were found beyond the area of excision, the presence of node involvement in the pathologic specimens was associated with a bad prognosis. Node metastases within confines of possible block excision probably should not be regarded as an absolute contraindication to radical surgery, but such a finding would obviously have to be weighed carefully in light of the site of the tumor and the condition of the patient.

Despite the findings that 75% of periampullary cancers in this series had no evidence of lymphatic or blood-borne spread at the time of resection, the majority of patients were dead within 5 years. Previous studies³ have clearly demonstrated the importance of blood-borne metastases particularly in the case of carcinoma of the pancreas. Because of the tendency of early widespread dissemination of cancer of the pancreas resulting in low resectability rates, emphasis has been placed on developing methods of early diagnosis including fiberoptic endoscopy, biochemical tests, angiography, and scanning techniques.¹¹

TABLE 8. *Comparison of Survivals: Adenocarcinoma versus Other Malignant Tumors of the Head of the Pancreas*

Type	Number of Cases	1 Yr	3 Yrs	5 Yrs	10 Yrs	15 Yrs
Adenocarcinoma	110	44.2%	10.2%	9.0%	3.8%	1.8%
Other tumors	10	70.0%	60.0%	40.0%	40.0%	10.0%

Although a 5-year survival rate of 18% has been reported, the results of radical surgery for carcinoma of the head of the pancreas have been poor.^{10,13-15} However, radical surgery still offers the only chance of cure to the patient, and, furthermore, up to 10% of other periampullary cancers with a relatively favorable prognosis may be mistaken for cancer of the pancreas. The incidence of cancer of the pancreas is increasing, and it is now the fourth leading cause of cancer deaths in the United States.^{5,12} Although there is little possibility of further advances in surgical technique, improvement in diagnostic and other methods of treatment are needed to combat periampullary cancer more effectively.

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DISCUSSION

DR. GEORGE L. JORDAN, JR. (Houston): Dr. Warren has been a strong proponent of an aggressive attack upon disease in this area, and I rise to support this contention.

Our experience with this disease is somewhat smaller than his, but our experience with 95 consecutive operations of this type for periampullary malignancies parallels his own series. Some of our patients were operated upon by some of our residents, and therefore our overall mortality rate is somewhat higher than his. But if we look at the patients operated upon by members of our faculty, the mortality rates are almost identical, because throughout our entire experience the mortality rate among that group has been 13.5%. Also, our survival rates are very similar.

Among all of our patients who have been operated upon more than three years ago, the three-year survival rate is 25%. This includes patients who died postoperatively, as well as the long-term survivors. Thus, there is a high salvage rate in this group, much higher than is generally appreciated.

Some of those patients who survived three years died before reaching the five-year period, but without disease. But we also have a significant number of five-year survivors.

I agree completely with his insistence upon categorization of the lesion. The best results we have obtained, as has he, are in patients with carcinoma of the ampulla of Vater, where our five-year survival rate is 37%.

Lastly, I would like to make a plea that I have made before to follow these patients carefully, and to attack vigorously any evidence of apparent recurrent disease, because it is too easy to presume that when the patient develops new abdominal symptoms, he now has recurrent carcinoma, and there's nothing else that one can do.

There have been a number of patients in our series who have been reoperated upon with symptoms of recurrent disease who were found to have benign disease which could be treated and salvage accomplished. There have been other patients who have developed a second, entirely separate, independent carcinoma which could be treated. One of our patients with carcinoma of the pancreas, for example, was not only a five-year survival following treatment of his carcinoma of the pancreas, but also a five-year survival following treatment subsequently of a carcinoma of the colon. Therefore, things are not always what they seem, and it behooves us to treat all of our patients aggressively, and to continue our treatment until we know that they have totally incurable disease.

DR. WILLIAM M. REMINE (Rochester, Minnesota): I rise in strong support of Dr. Warren and his philosophy regarding carcinoma of the pancreas, duodenum, and ampulla, because, as he indicated there, the mortality in the untreated cases is very high. We have summarized our experience with pancreatoduodenectomy in 1963 with 239 cases, and at that time we had an 18% five-year survival of head lesions. One of these

was a malignant lesion of the islet of Langerhans, and we felt that it was worthwhile to pursue the problem further even though the survival was low and there was lots of room for improvement.

We, therefore, began to look at the possibility of total pancreatectomy, because of the inability to detect the outer limits of the lesion as it expands into the head of the pancreas, and also because of the possibility of multicentric lesions.

In 1970 we summarized our experience with total pancreatectomy, and at that time we had 36 cases. Since then, we have summarized our experience again recently with 28 more cases for a total of 64 patients treated with total pancreatectomy.

I'd like to give you just a few of our findings in that series. Initially we had a 27% five-year survival with total pancreatectomy. The series was small, and so we don't know that it is highly indicative, except that it's encouraging.

In the more recent series we have reduced our operative mortality, which was originally 16% through 1968. From '68 to '70 it was reduced to 11%, and since 1970 it's been 7.4%. We feel this is a marked improvement and a better selection of patients. Prior to 1968 we were operating on patients with very large lesions that required total pancreatectomy for their removal.

In the total series, the longest survivor in the group, with adenocarcinoma of the pancreas, lived six years and eight months. There is a patient still alive who had rhabdomyosarcoma who has remained alive for 14 years after removal, and, since then, he's had another operation subsequently for a stricture of the hepaticojejunostomy. I think this man would have been written off as a recurrence if we had not operated on him with the hope of being able to do something for him.

Of the nine patients with ampullary carcinoma, the longest survivor remains alive 6½ years after total pancreatectomy. Two patients survived three or more years, and four patients remained alive for one or more years. There were four patients with cystadenocarcinoma; the longest survivor lived about five years, or four years and nine months.

I would like to ask Dr. Warren if they have checked their specimens for evidence of multicentricity. When we went over ours we found that nine of the patients with total pancreatectomy with malignancies had multicentric lesions. We feel this is very important if you are going to eradicate all of the malignant problem. If so, what percentage did they have?

I think the high degree of pessimism in certain quarters with regard to this problem is totally unwarranted. I feel we need to strive more diligently in this direction if we are going to get people well. I think earlier diagnosis, of course, is the key to the whole problem.

DR. GEORGE CRILE, JR. (Cleveland): I think it's generally recognized that there is a striking difference in prognosis between gastrointestinal tract tumors that are polypoid and those that are invasive and ulcerating. This has certainly been true in our experience in the ampullary lesions. We have only one long-term survivor of an infiltrating, as opposed to a polypoid tumor.

This makes a lot of difference if you are dealing with older and debilitated people, because it's too bad to run a great risk of immediate death by doing a big operation on someone who has very little chance of being cured. So if you can select the polypoid tumors, you are ahead. I think we can do that today by the technique described by my associate, Dr. Esselstyn, namely, at the time of operation, if your endoscopist is not able to routinely visualize the ampulla, you can guide his scope to the ampulla and evaluate this without running any risk of contamination of the peritoneal cavity.

I have been very much impressed with the mortality rates that have been quoted, but I think it would be unfair not to point out that these are not average mortality rates. The average mortality for the radical operation in the professional hospital audit is reported at 32%.

If your patient can live a little longer and have more years of life with a conservative operation rather than a radical one, in selected cases that may be best.

DR. KENNETH W. WARREN (Closing discussion): I want to thank each discussant. I shall start with Dr. Crile. I agree with him that all of us die sooner or later. We were on a panel together in New York recently, and he said "Death is never a victory." I told him it was if you went to heaven.

We did not break down the long-term results of various types of ampullary carcinoma. They can be polypoid, flat and invasive; they can invade the head of the pancreas and make it impossible to determine the precise origin. The distinction is very complex and relates primarily to the modes of spread.

I agree with him that if a person is very ill, old, and an extremely poor risk, and the tumor is of questionable resectability, I would do a bypass. One thing I neglected to say: if a patient has exploratory laparotomy and nothing is done—but has diffuse carcinomatosis—these patients

live an average of five months. If they have a bypass procedure, they live an average of nine months. If they have a resection for ductal carcinoma of the head of the pancreas, the mean survival is 15 months.

Endoscopy is important. We do endoscopic studies frequently, but would almost never reject a patient for operation upon endoscopic findings. Endoscopy may give valuable information, but it is not definitive.

Total pancreatectomy—we went around this horn many years ago—and as I have told Dr. ReMine before, I think one of the reasons we got discouraged was probably because we were applying total pancreatectomy at that time to patients who should not have had the tumor resected at all. We must keep an open mind about this procedure and see what the survival rates are after many patients have had followup studies for many years. In evaluating total pancreatectomy, we must know the precise cell type of these tumors.

Dr. ReMine, I cannot tell you the percentage of multicentric tumors. We do not recognize multiple tumors. We often reject some of them because of multicentric involvement associated with other evidences that indicate that they probably are not suitable for resection.

I do not like the argument advanced by some surgeons that a total pancreatectomy will have a lower operative mortality because it is not necessary to anastomose the pancreatic duct. The pancreatic duct, properly anastomosed, is not a real problem.

Dr. Jordan, I think the fact that he has an attitude that parallels ours explains the reasons that his statistics parallel ours. The most pertinent thing that Dr. Jordan said that would correlate with our experience is the urgency for not writing off these patients when they have recurrent abdominal symptoms, unless they have very obvious evidence of recurrence and perhaps even diffuse recurrence. This applies particularly to those patients in whom jaundice may develop many years later and may have a benign stricture of the choledochojejunostomy.

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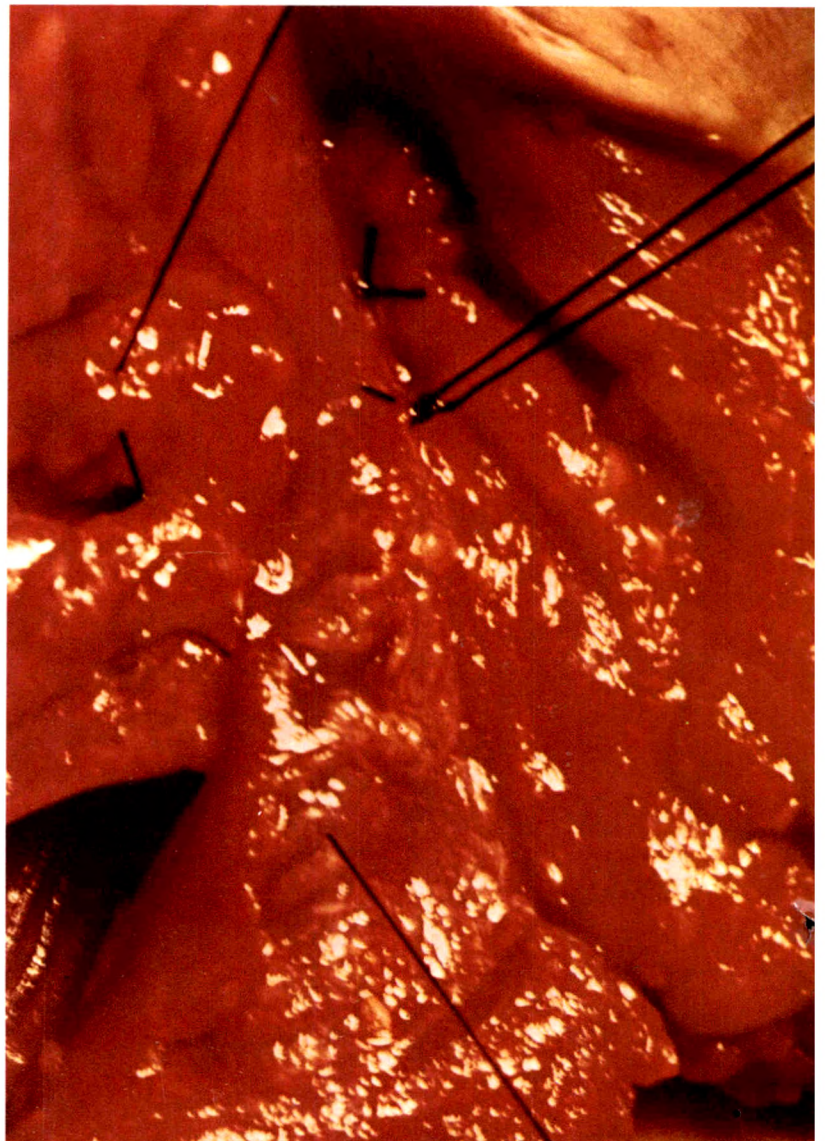
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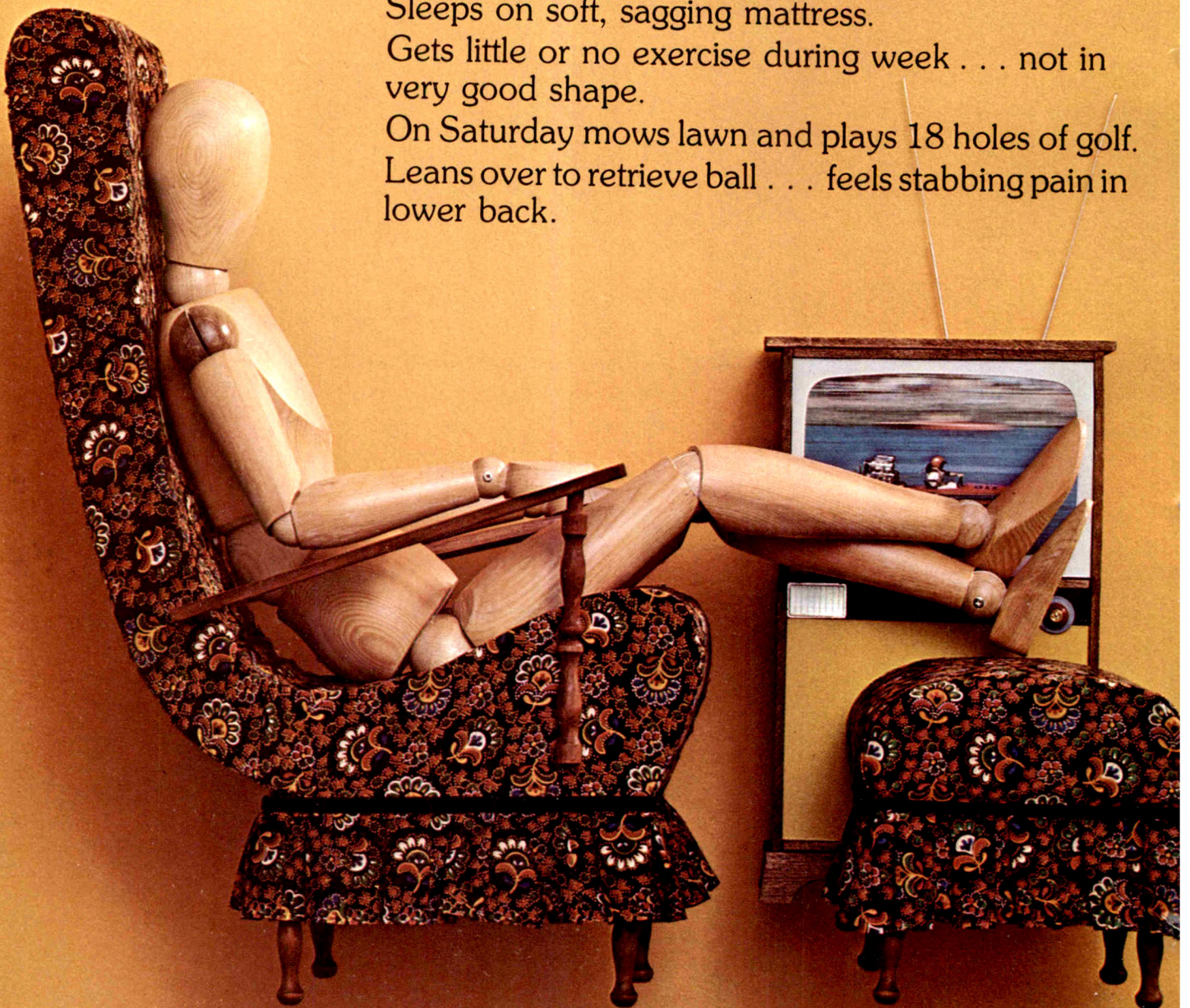
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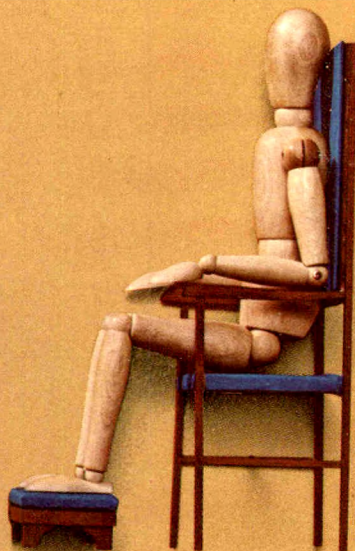
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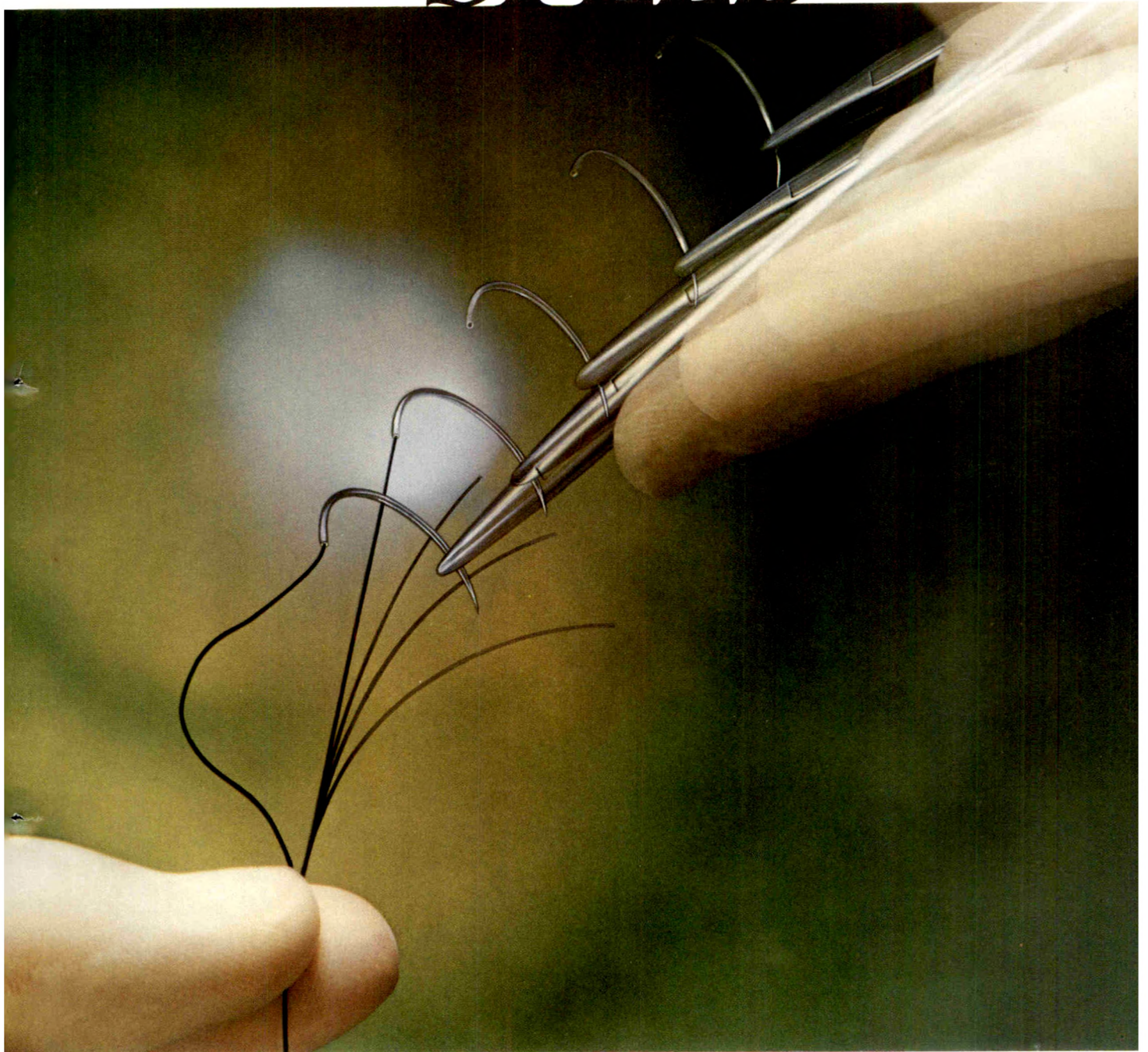
By **ALAN R. MORITZ, M.D.** and **R. CRAWFORD MORRIS, L.L.B.**; with the assistance of **CHARLES S. HIRSCH, M.D.** February, 1975. 286 pages plus FM I-XII, 5½"x 8½", 35 illustrations. Price, \$10.25.

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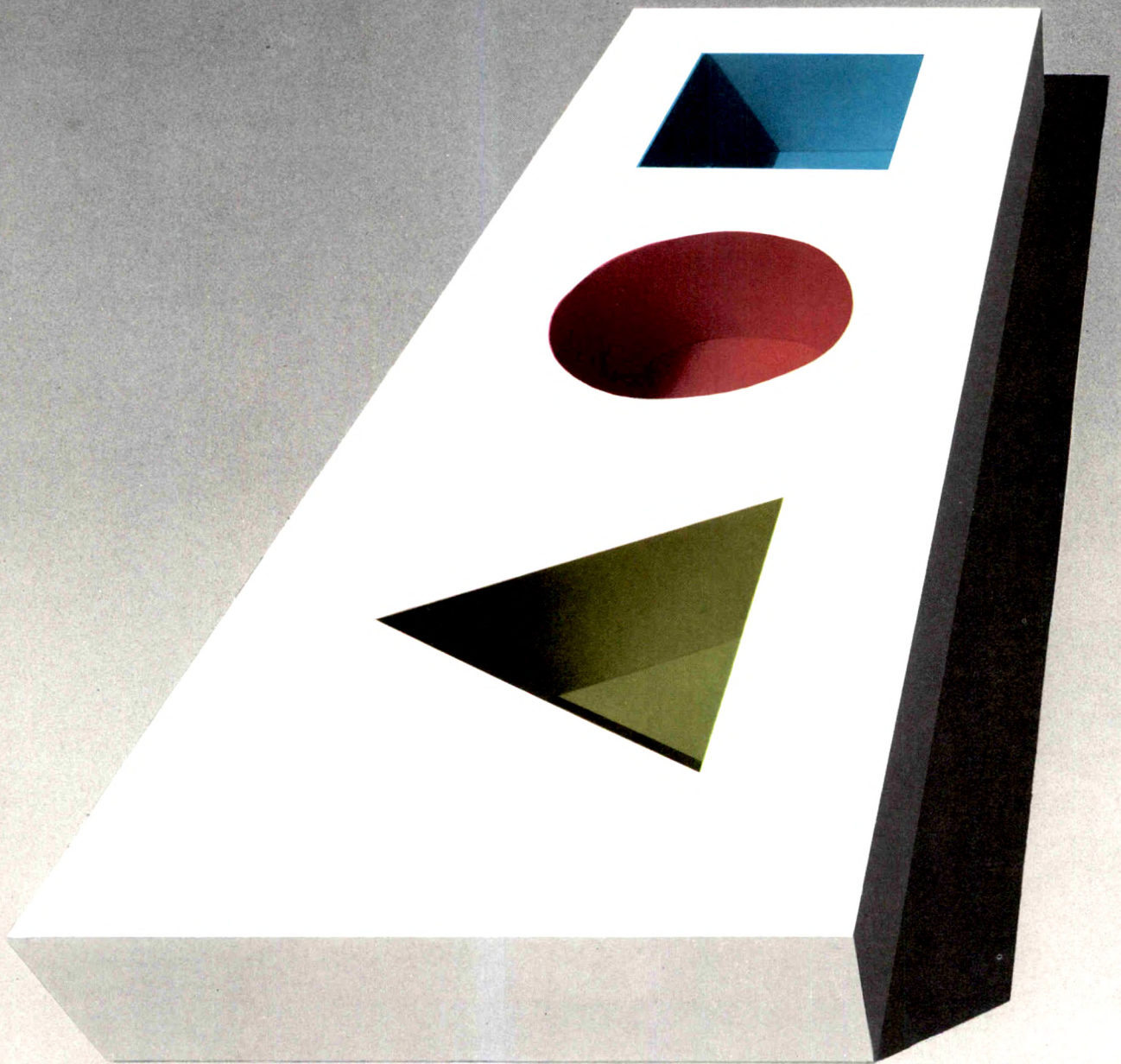
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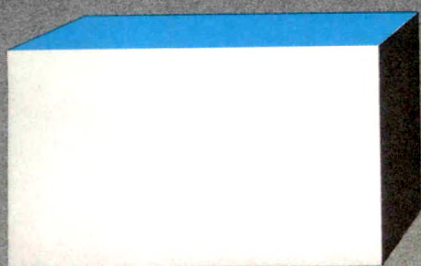
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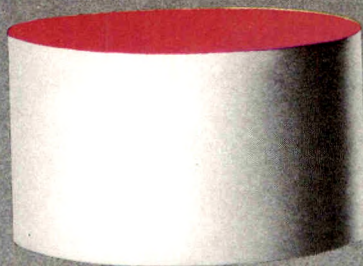


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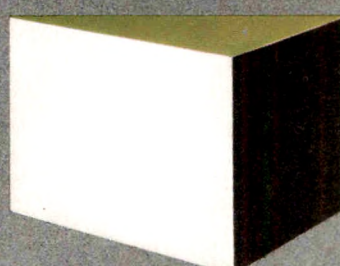


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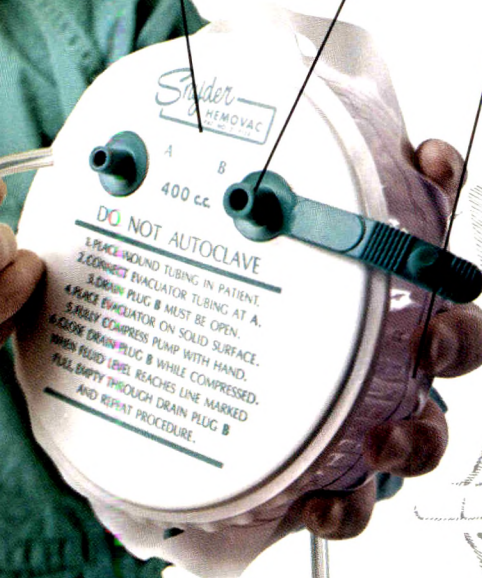
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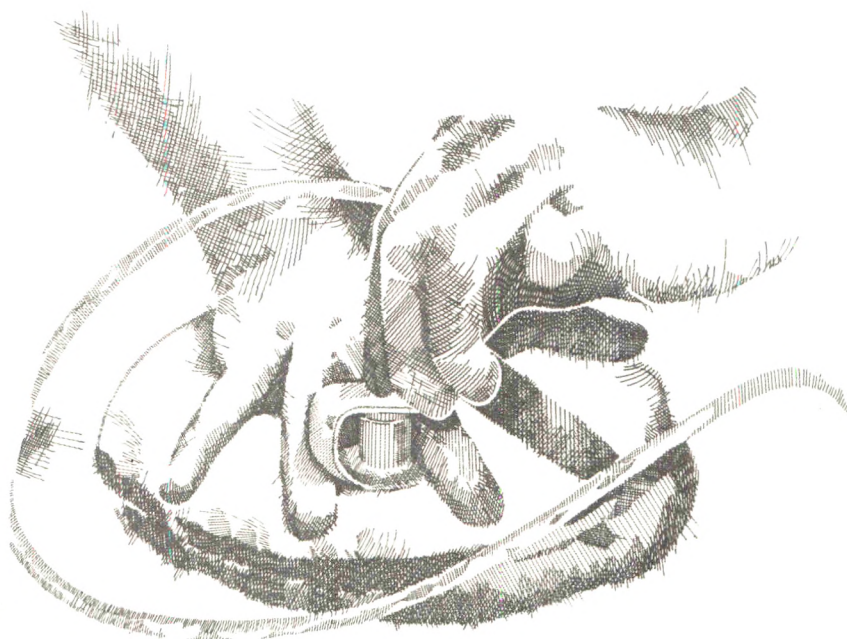
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may be implicated
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- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena



Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, non-sporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

Under normal conditions, **bacteroides** are benign. But in infectious situations they can be extremely virulent.

Fortunately, most **bacteroides** infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a **Bacteroides** infection is present. Chloromycetin must be used only in those serious infections for which less potentially dangerous

drugs are ineffective or contraindicated. But when bacteroides are detected, Chloromycetin (chloramphenicol) therapy is indicated. In conservative conditions, the bacteroides can be treated with Chloromycetin. See next page for information.

Bacteroides...

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WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by

in vitro studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**

It is not recommended for the routine treatment of the typhoid carrier state.

2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.

- a) *Salmonella* species
- b) *H influenzae*, specifically meningial infections
- c) Rickettsia
- d) Lymphogranuloma-psittacosis group
- e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
- f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents

3. Cystic fibrosis regimens

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
 - (1) abdominal distention with or without emesis;
 - (2) progressive pallid cyanosis;
 - (3) vasomotor collapse, frequently accompanied by irregular respiration;
 - (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled *Gray Syndrome under Adverse Reactions.*)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants. This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

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Pancreaticogastrostomy:

A Further Evaluation

JULIUS A. MACKIE, M.D., JONATHAN E. RHOADS, M.D., C. DICK PARK, M.D.

*From the Harrison Department of
Surgical Research, University of
Pennsylvania, Philadelphia, Pa.*

The anastomosis between the remaining pancreas and the intestinal tract after various types of pancreatic resection has been the site of complications responsible for considerable morbidity and mortality. After Whipple resections reestablishment of pancreatic-intestinal continuity has generally been accomplished in some manner between the pancreas and upper jejunum. This suture line has at times failed, often as the result of postoperative pancreatitis, giving rise to hemorrhage, abscess, and fistula formation. Since 1963, 25 patients undergoing pancreaticoduodenal resection have had some portion of their pancreas implanted into the back wall of the stomach. The operations have been done by the resident and senior staff of the Department of Surgery at the University of Pennsylvania. Morbidity has decreased and operative mortality has fallen from 20-30% to 8%. The technique is not difficult and there seems to be less tendency for the anastomosis to leak. Pancreatic function is usually adequate. The procedure is useful after radical resection of the pancreaticoduodenal region or at times after pancreatic trauma.

FOR MANY YEARS, postoperative deaths following pancreaticoduodenal resection occurred with great frequency. Operative mortality was in the range of 25-30% or above. However, in 1968 Howard reported a personal experience of 41 resections without an operative death. At the present time, operative mortality in several large centers is now around 10% or under. Other series still realize a death rate somewhat higher.

Difficulties with the remaining pancreas have usually been responsible for a major portion of serious postoperative complications and mortality. Removal of the entire pancreas obviates this problem to a great extent, but even with intensive endocrine and exocrine replacement, these patients do not thrive as well as those who still have part of their pancreas intact. After Whipple

resections, reestablishment of pancreatic-intestinal continuity has generally been accomplished in some manner between the remaining remnant of pancreas and the upper jejunum. This anastomosis has often failed, giving rise to fatal complications. Postoperative pancreatitis is, no doubt, part of the process that so often leads to hemorrhage, abscess, and fistula formation, originating at the pancreaticojejunostomy. Ligation of the duct of Wirsung with closure of the stump of the pancreas has also been unsatisfactory.

Pancreaticogastrostomy is an alternative method of restoring pancreatic-intestinal continuity which has been employed by members of the Department of Surgery of the University of Pennsylvania since 1963. The original animal and clinical experimental work on this problem was discussed in a previous publication.^{4,6}

The purpose of this study was to evaluate 11 years experience with pancreaticogastrostomy after radical resection of the pancreaticoduodenal region from the standpoint of operative mortality and postoperative complications, specifically those related to the remaining pancreas.

Clinical Data

From February 1963 through September 1974, 25 patients have undergone the Whipple operation and have had the remaining pancreas anastomosed to the back wall of the stomach. There have been two postoperative deaths, an operative mortality of 8%. Data for these patients are summarized in Table 1.

The first postoperative death occurred in patient J. H. who developed a fulminating postoperative pancreatitis

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1974, Boca Raton, Florida.

Reprints requests: Julius A. Mackie, M.D., Harrison Department of Surgical Research, University of Pennsylvania, Richards Building—Hamilton Walk, Philadelphia, Pennsylvania 19174.

TABLE 1. *Operative Mortality—1974**

Tumor site	Number of Patients	Deaths
Pancreatic Head	13	
Ampulla of Vater	8	1
Duodenum	2	1
Chronic Pancreatitis	2	
	25	2

*Operative mortality: 8%

following resection of duodenal carcinoma. The entire pancreas sloughed, resulting in overwhelming sepsis and death. An error in management caused the second death of patient, F.S., who had an ampullary carcinoma resected. This patient developed a bile peritonitis when the T-tube was inadvertently clamped during the first 12 hours after surgery. The bile peritonitis became secondarily infected and the end result was an intraperitoneal hemorrhage with cardiac arrest on the 12th operative day. At postmortem examination the pancreatic anastomosis was still intact (Table 2). It should be noted that two of the patients thought to have carcinoma of the head of the pancreas had chronic pancreatitis after the final histological examination.

There were three nonfatal complications in the series. Patient H. W. developed a pancreatic anastomotic leak following an episode of acute dilatation on the first day oral fluids were administered. A sump drain was inserted and the fistula closed promptly. Two other patients had biliary cutaneous fistulae which closed without incident with sump suction after a short period of time.

The operative mortality from the world literature including our own experience is shown in Table III. Only four operative deaths have been reported including two from our own series for an overall mortality of 8%. Only one of the 4 deaths related to the pancreatic anastomosis.

Postoperative studies and postmortem examinations have demonstrated patency of the pancreatic duct as long as 11 months after the original surgery.⁶

TABLE 2. *Operative Deaths and Complications*

Patient	Age, Sex	Tumor Site	Complications
SH	49, M	Duodenum	Postoperative Pancreatitis—Died
ES	63, F	Ampulla	Bile Peritonitis—Died
		Deaths: 2	
HW	68, M	Head	Pancreatic Anastomotic Leak—Survived
CM	67, F	Ampulla	Biliary Cutaneous Fistula—Survived
LR	51, M	Pancreatitis	Biliary Cutaneous Fistula—Survived
		Non-fatal Complications: 3	

TABLE 3. *Operative Mortality for Pancreaticogastrostomy After Radical Pancreaticoduodenectomy*

Author and Year	Number of Cases	Operative Deaths	% Operative Mortality
Waugh & Clagett 1946 ¹⁰	1	0	0
Wells, Sheper & Gibbon 1952 ¹¹	3	1	33
Dill-Russell 1952 ²	2	1	50
Ingebrigtsen & Langfeldt 1952 ⁹	2	0	0
Sames 1952 ⁸	1	0	0
Nanson 1954 ⁵	1	0	0
Silverstone 1956 ⁶	1	0	0
Millbourn 1959 ⁴	7	0	0
Pataky & Popik 1959 ⁷	1	0	0
Hurwitz 1967 ¹	6	0	0
Hospital of the University of Pennsylvania 1974	25	2	8
	50	4	8

Operative Technique

After the body of the pancreas has been divided and the line of transection proven free of tumor, the remaining pancreas is closed with interrupted sutures of 3-0 silk. It is important not to obliterate the pancreatic duct. Several of the silk sutures are left long and used to draw the pancreas through the gastrostomy into the stomach during the anastomosis. Approximately 2-3 cm of pancreas should be freed up from the retroperitoneal attachment to

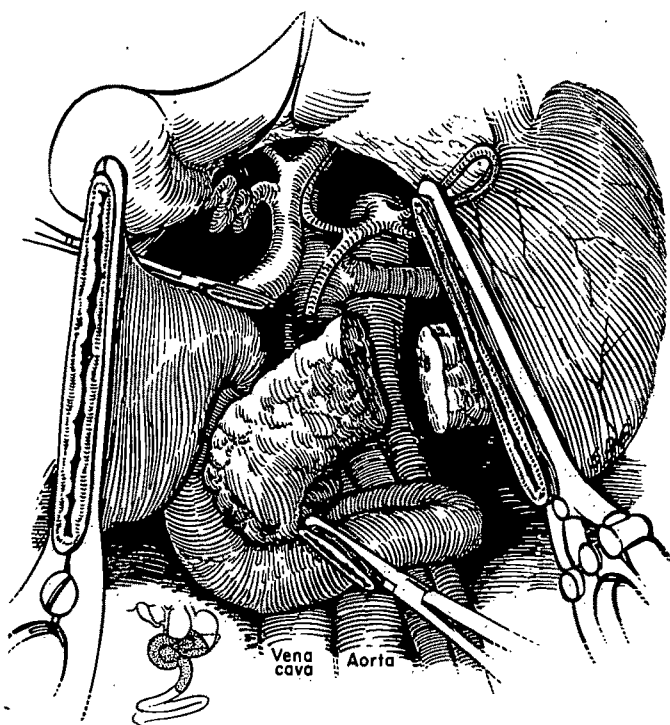


FIG. 1. Pancreaticogastrostomy—showing extent of resection.

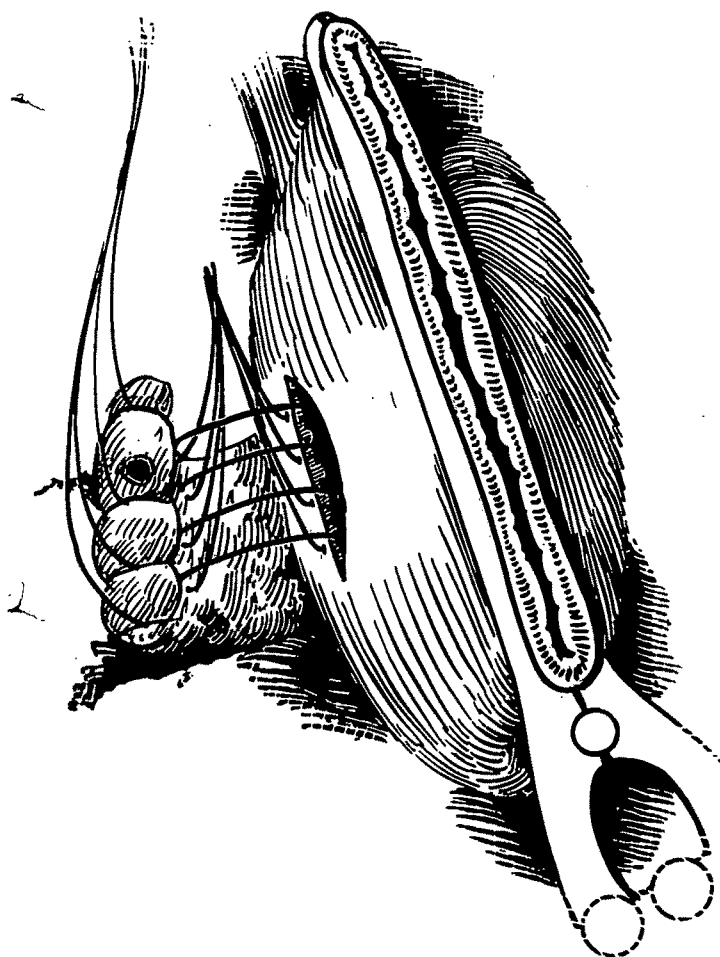


FIG. 2. Opening in the posterior wall of the stomach and row of silk sutures between anterior surface of pancreas and left lateral side of gastrotomy.

allow a sufficient amount of the gland to project into the stomach (Figs. 1 and 2).

A 50-60% distal gastrectomy provides enough proximal stomach to permit an easy approximation to the remaining pancreas. After division of the stomach between Payr clamps or clips inserted with an automatic suturing instrument, traction on the proximal stomach is released to allow approximation of the pancreas to the posterior wall without tension. An interrupted row of 3-0 silk is employed between the anterior serosal surface of the pancreas and the posterior wall of the stomach. A gastrotomy incision 2-3 cm in length is made in the posterior wall of the stomach (Fig. 2). This should be sufficiently proximal to the site of the intended gastroenterostomy to avoid complicating the anastomosis. The long ends of the silk suture used to close the pancreas are threaded on a straight needle and passed through the incision in the posterior wall and out the anterior wall of the stomach (Fig. 3). Traction on these sutures holds the cut end of the pancreas securely within the lumen of the stomach while the remainder of the posterior row of interrupted

silk sutures is put in place to complete the outside layer (Fig. 4). The stomach is opened and the anastomosis visualized from within the lumen. A second layer of continuous, locked 2-0 chromic catgut suture approximates the gastric mucosa to the pancreas within the lumen of the stomach (Fig. 5). On completion of this suture line, the silk sutures on the cut end of the pancreas are cut short and about 1½-2 cm. of pancreas should project into the lumen of the stomach without tension. The biliary anastomosis is then accomplished followed by a gastro-jejunostomy distal to it. Sump drains are placed to the right and left of the pancreaticogastrostomy posterior to the stomach (Fig. 6).

Gastrosopic observations and postmortem studies have shown that the intra-gastric portion of pancreas disappears either by sloughing or retraction and that gastric mucosa grows to the pancreatic duct, leaving its patency preserved.

Discussion

Current diagnostic techniques have not improved the curability of carcinomas of the pancreaticoduodenal re-

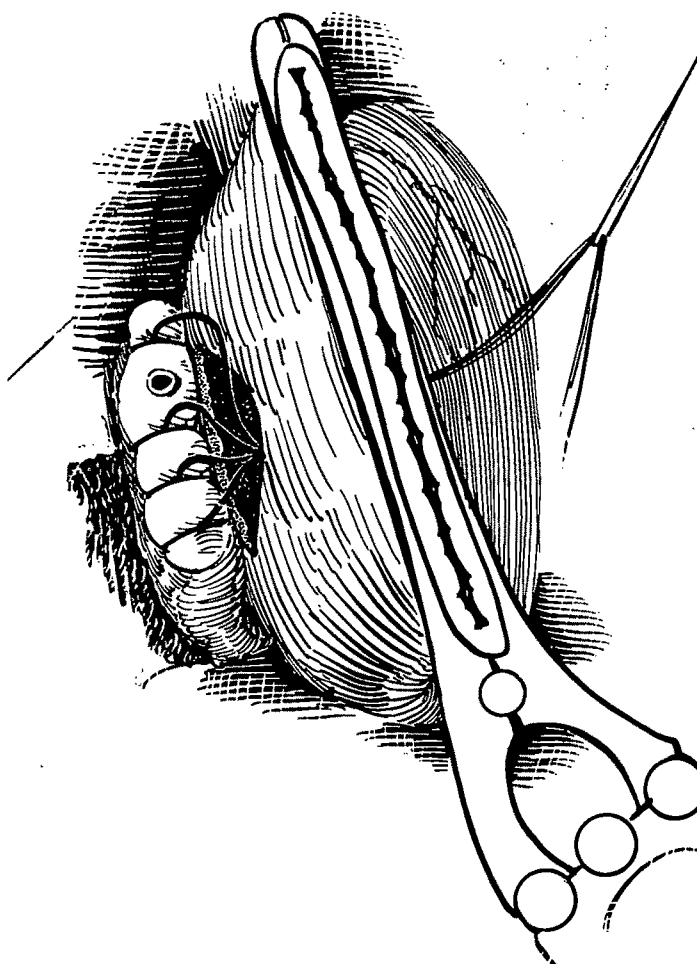


FIG. 3. Use of long end of sutures on the cut end of pancreas to draw the pancreas through the gastrotomy into the lumen of the stomach.

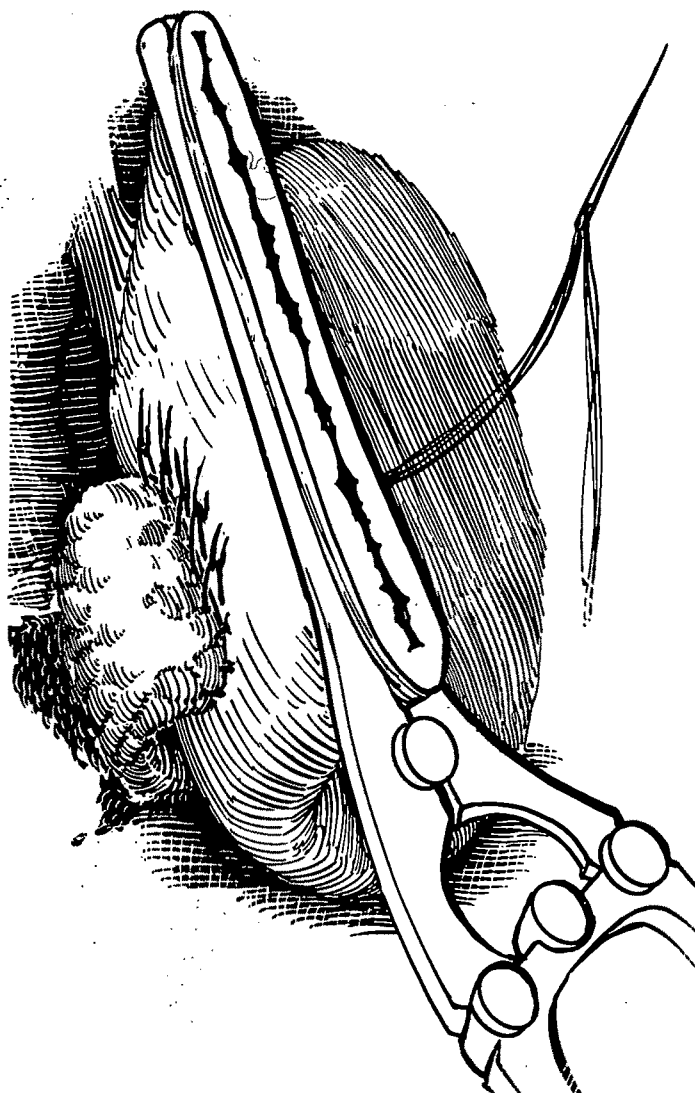


FIG. 4. Placement of silk sutures between the right edge of the gastrotomy and posterior wall of the pancreas.

gion. Usually, more effective palliation is achieved by resection than by bypass procedures, provided morbidity and mortality are not prohibitive.

Implantation of the pancreas into the stomach has lowered operative mortality in this institution from over 25% to 8% in the past 11 years. The operations have been performed by surgeons of varied experience, including the resident staff and not by one single surgical team.

The anastomosis is easy to accomplish technically. The pancreas lies in natural apposition to the posterior wall of the stomach. Sutures between the pancreas and the stomach seem more secure than between the pancreas and the jejunum since the stomach has a thicker wall and the anastomosis can be reinforced from within the lumen of the stomach.

The acid pH in the stomach is unfavorable for proteolytic activity. Pancreatic enzymes flow into the gastrointestinal tract proximal to the small bowel enzymes

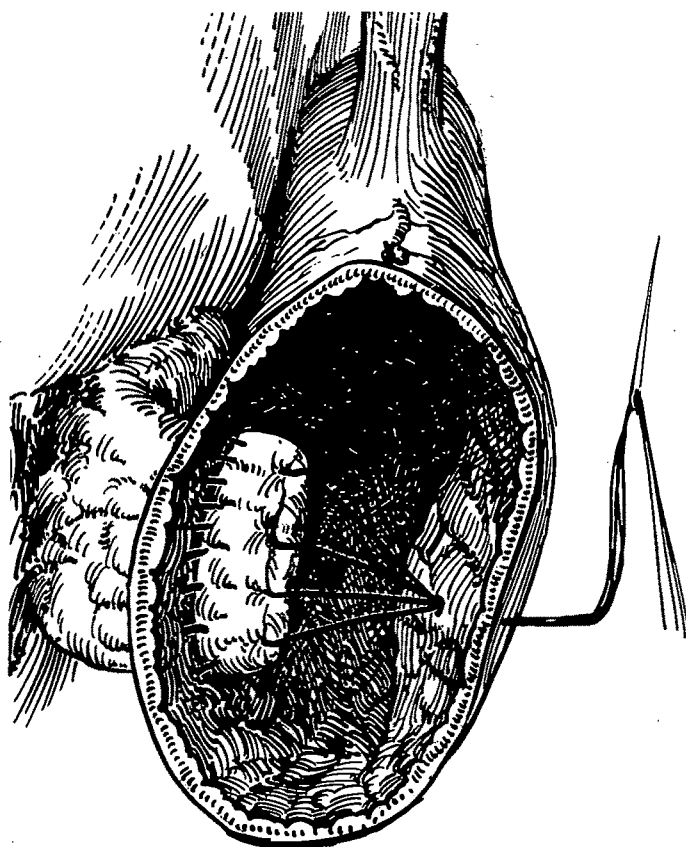


FIG. 5. Intraluminal suture of the pancreas to the gastric mucosa through the open end of stomach.

which activate trypsinogen and chymotrypsinogen. These factors tend to lessen the chances of postoperative pancreatitis and autodigestion with hemorrhage, fistula and abscess formation.

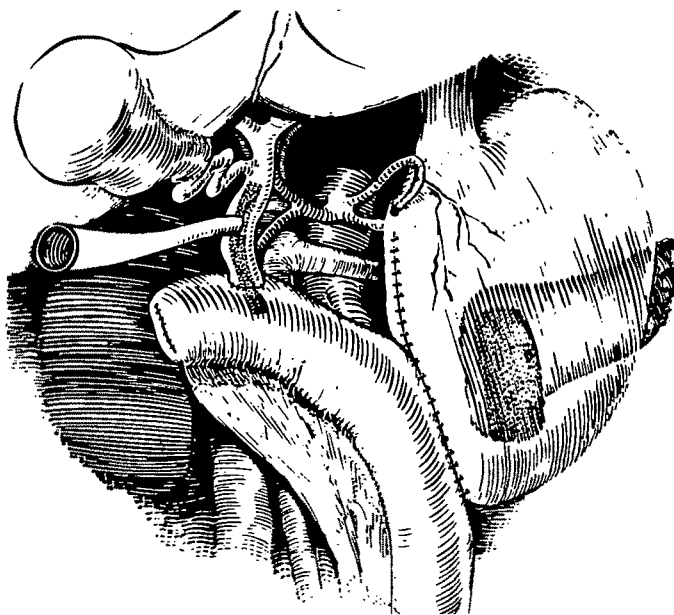


FIG. 6. Reconstruction of biliary, pancreatic and intestinal continuity.

Some patients may show varying degrees of pancreatic insufficiency postoperatively. This depends on the amount of functioning pancreas remaining rather than on an anastomotic obstruction.

Implantation of the pancreas into the stomach has been employed satisfactorily in patients with trauma or chronic pancreatitis, as well as those undergoing the Whipple operation for malignancy.

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DISCUSSION

PRESIDENT SABISTON: As is recognized, this technique which Dr. Rhoads has presented is an original contribution from the University of Pennsylvania. Its use has recently been emphasized by others, and it is particularly appropriate to have this series updated by the originators of the method.

DR. GEORGE H. BUNCH, JR. (Columbia, South Carolina): I would like to recount briefly one experience that I had one night last week. I received a call to come see a patient with massive upper G. I. bleeding. This had been going on for twelve hours and during this time his blood pressure had hit zero twice; he had had a "mayday" on his last episode, and they thought that perhaps surgery might be necessary.

As we prepared the patient for surgery, one thing bothered me—he said that he was operated upon by Dr. Bill ReMine about two years ago, and he had a pancreatic cyst drained. We thought he had a Roux-Y drainage.

I quickly tried to find Bill in the middle of the night on an emergency call telephone number, but I couldn't find it. So we took him to surgery, and to make a long story short, we opened the duodenum—no point for bleeding was found; opened the stomach widely—no point for bleeding, but blood was everywhere. Under the circumstances we thought, probably, a vagotomy and high gastrectomy would be the best we could do. This sounded pretty simple.

We approached the stomach again. We found that the pancreatic cyst had been drained into the posterior wall of the stomach rather than by Roux-Y and this had completely healed over. There was no recurrence of the cyst. But when we began to try to take this stomach out, which sounds like not too much of a procedure, it was found to be like a bag of wet cement that had been poured in there. There was no way of separating it from the pancreas or the liver. Doing a vagotomy was out of the question. We could hardly even find the diaphragm.

We did, after a long struggle, get out about 60% of the patient's stomach without vagotomy, and yesterday he was doing reasonably well.

DR. JULIUS A. MACKIE (Closing discussion): We have felt that the current diagnostic techniques for carcinomas of the peripapillary region have really not improved the curability of this problem after surgery. We have also been of the opinion that in comparable patients more effective palliation is accomplished by end resection, rather than by a bypass procedure, provided the operative morbidity and mortality is not prohibitive.

As Dr. Rhoads pointed out, the implantation of the pancreas into the stomach has reduced our mortality considerably, from over 25% to 8%; and it should be emphasized that these procedures have been done quite frequently by members of the resident staff, and, in fact, neither of the two deaths which were reported occurred in patients done by the residents. Perhaps they should do them all.

The anastomosis is easy to accomplish technically, since the pancreas lies in natural apposition to the posterior wall of the stomach. Sutures between the pancreas and the stomach seem a bit more secure, since the stomach wall is thicker, and also since we can reinforce this anastomosis from within the lumen of the stomach.

We have wondered why it seems better in our hands. Perhaps it's because the acid pH of the stomach is unfavorable for proteolytic activity. These pancreatic enzymes flow into the gastrointestinal tract proximal to the small bowel, whose enzymes activate trypsinogen and chymotrypsinogen. These factors, we think, tend to lessen the post-operative pancreatitis, which causes hemorrhage, abscess and fistula formation.

Some of the patients may show varying degrees of pancreatic insufficiency postoperatively. This seems to depend on the amount of functioning pancreas that remains, rather than any obstruction at the anastomosis.

Changing Patterns in the Management of Pancreatic Pseudocysts

PAUL R. HASTINGS, M.D., FRANCIS C. NANCE, M.D., WALTER F. BECKER, M.D.

The records of patients treated from 1938 through June, 1974, for pancreatic cysts have been reviewed. There were 205 cysts including 168 pseudocysts, 21 neoplastic, 13 retention, and 3 congenital cysts. Operative procedures were performed in 154 patients with pseudocysts. An analysis of two eras has been made: cysts treated prior to 1962 (56 patients) and cysts treated after 1962 (98 patients). In the earlier era 66.4% of patients were treated by external drainage and 34% by excision or internal drainage. By marked contrast in the more recent era only 27% were treated by external drainage and 73% by excision or internal drainage. The recurrence rate fell from 27% in the earlier era to 6% in the modern era. Improved morbidity was evidenced by a reduction from 32.2% to 15.3% in additional procedures required. Individualization in the treatment of pseudocysts with adherence to establish criteria for procedure selection with increased reliance on excision or internal drainage, as well as early diagnosis and timely intervention have improved the results of surgical therapy in this disease.

SUCCESSFUL SURGICAL THERAPY of a pancreatic cyst was first accomplished in 1881 by Bozeman³ who excised a true cyst of the pancreas. In 1882 Gussenbauer⁷ was the first to successfully manage a pancreatic pseudocyst by marsupialization. Since that time several operative procedures have been developed for the treatment of pancreatic pseudocysts.^{4,11} The management of pancreatic pseudocysts has been surgical because spontaneous resolution is rare and the complications of infection, hemorrhage, and rupture that accompany procrastination are disastrous.^{1,2,4,6,8-11}

Pancreatic pseudocysts are uncommon in any individual surgical practice. A collective series of patients is necessary for quantitative evaluation of therapy of this disease. For the present study, the records of patients treated from 1938 through June, 1974, at four New Orleans hospitals were reviewed. Two hundred five case

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records of patients with pancreatic cysts including 168 pseudocysts, 21 neoplastic cysts, 13 retention cysts, and 3 congenital cysts were collected. Operative procedures were performed on 154 patients with pseudocysts (56 before 1962 and 98 since 1962). In our review and analysis, we have identified a transition in the pattern of surgical therapy. When patients treated before 1962 (Group I) were compared with those treated after 1962 (Group II), a significant shift in surgical management towards internal drainage could be seen. The results of this change have been analyzed and will be discussed.

Clinical Material

There were 100 males and 54 females. Seventy-nine patients were Caucasian and 75 Negro. The age range was from 4 to 84 years. The mean age was 45 and the median age was 43 (Fig. 1). Pseudocysts were most common during the fourth and fifth decades corresponding to the peak incidence of pancreatitis.

Associated Diseases

The exact etiology for development of a pseudocyst is unknown. Several factors appear to be contributory. Among the 154 operative cases, pseudocysts were associated with alcoholism in 55 patients, cholelithiasis in 33, diabetes mellitus in 10, carcinoma of the pancreas in 2, pregnancy in 2, and sickle cell disease in 1. Three patients had associated severe chronic renal failure. Hypercalcemia and/or hyperparathyroidism were not present in any of the cases.

Pseudocyst development was preceded by pancreatitis in 129 cases. In 25 cases no definite underlying pancreatitis could be established. The pancreatitis was acute

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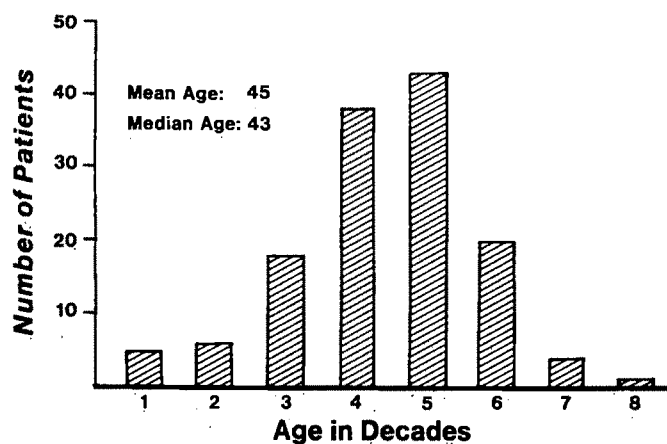


FIG. 1. Pseudocysts of the pancreas.

in 51 patients, chronic in 52, and traumatic in 26. Of the patients who had traumatic pancreatitis, 20 had had blunt trauma, 2 had had a gunshot wound of the abdomen, and 4 had had peripancreatic operative trauma.

Clinical Findings

Pain, nausea and/or vomiting and weight loss were the most common symptoms (Table 1). Abdominal tenderness and palpable mass were the most common signs (Table 2).

Jaundice, which was present in 10% of patients, proved to be secondary to pancreatitis and cyst compression of the common bile duct and peri-ampullary region in 14 patients. Four patients had associated cholelithiasis. Two additional patients had jaundice as a result of coexistent carcinoma of the head of the pancreas.

In 168 patients including those who died without an operation, 23% had 45 serious complications of rupture, infection, or hemorrhage into the pseudocyst (Table 3). Rupture was associated with a 60% mortality, hemorrhage with a 17% mortality, and infection with a 21% mortality (Table 4).

Laboratory and X-ray Findings

An elevated serum or urinary amylase was present in 87 of 154 patients (57%). Leukocytosis (WBC greater

TABLE 2. Presenting Signs in 154 Operative Cases

	Number of Patients	Percent
Tenderness	112	72.6
Mass	100	65.0
Fever	42	27.3
Jaundice	16	10.4
Hemorrhage	10	6.5
Ascites	3	1.9

than 10,000) was found in 74 patients (48%). Anemia (hematocrit less than 35%) was present in 44 patients.

Radiographic examination proved to be the most helpful diagnostic tool. Chest X-ray revealed 19 cases with a pleural effusion, 17 on the left, one on the right, and one bilateral. Abdominal plain films revealed a mass in 20 patients, pancreatic calcifications in 14, segmental ileus in 4, and displacement of the gastric air bubble in 1 patient. Cholangiography demonstrated associated biliary pathology in 21 patients.

Displacement of stomach or duodenum seen on upper gastrointestinal series suggested the diagnosis of pseudocyst in 87 patients. Barium enema showed colon displacement by a mass in 21 patients. Selective arteriography was employed only occasionally, generally not adding other than confirmatory evidence of a mass previously demonstrated by other means. Its use in experienced hands for diagnostic confirmation of pancreatic masses in difficult cases might prove valuable. Ultrasound was employed in 2 patients in the last few months of our survey, and was indicative of a nonsolid mass in both cases.

Treatment and Results

Nonoperated Patients

Of the 168 patients with pseudocysts, 13 were identified at autopsy. An additional patient had the diagnosis established at the time of an incisional hernioplasty, but primary treatment was deferred. This patient was unfortunately lost to followup. In Group I (pseudocysts encountered before 1962), 6 of the 8 deaths in nonoperated patients could be attributed directly to complications of the pseudocyst. In Group II (pseudocysts encountered beginning with 1962), 2 of the 5 deaths could be attributed

TABLE 1. Presenting Symptoms in 154 Operative Cases

	Number of Patients	Percent
Pain	138	89.6
Nausea and/or Vomiting	95	61.7
Weight Loss	78	50.7
Mass	44	28.6
Fever	36	23.4
Jaundice	12	7.8
Diarrhea	9	5.8
Hematemesis or Melena	6	3.9

TABLE 3. Complications in 168 Patients

	Number of Patients	Complications
Hemorrhage	8	8
Infection	24	24
Rupture	1	1
Infection and Hemorrhage	2	4
Infection and Rupture	2	4
Rupture and Hemorrhage	2	4
Total	39	45

TABLE 4. *Mortality as Related to Complications*

Complication	Number of Patients	Percent	Mortality	Percent
Infection	28	16.7	6	21.4
Hemorrhage	12	7.1	2	16.7
Rupture	5	3.0	3	60.0

to the pseudocyst. The remainder of these patients died of unrelated causes (Table 5). In the modern era operative salvage has been attempted despite grave complications, whereas 10% of the patients in the earlier era died of complications without surgery.

External Drainage

External drainage was used as primary treatment in 63 of the 154 operative cases (Tables 6, 7, and 8). It was used in two-thirds of the patients (66%) in Group I but only a quarter (27%) of the patients in Group II. The overall recurrence rate was 29%, and the overall mortality rate was 11%.

In Group I there were two postoperative deaths following marsupialization. One patient died two months after operation. Massive hemorrhage occurred from the cyst and gastrointestinal tract. The other patient died of massive hemorrhage 10 years postoperatively following an excision of a recurrent cyst. There were 5 deaths in Group II. Two of these patients had an infected pseudocyst, and 1 had an infected, ruptured pseudocyst. Two of these patients died from multiple pulmonary emboli, and the other died of sepsis and hemorrhage from the cyst. A fourth patient died of massive bleeding into the cyst, and the last patient died of carcinoma of the pancreas and cardiac disease.

Additional procedures were required for complications in 32% of the patients treated by external drainage. The major indications for additional surgery were recurrence, persistent pancreatic fistula, and hemorrhage from the cyst and/or the gastrointestinal tract. The overall complication rate was 41% (Table 9).

Excision

Excision of the cyst was accomplished in 20 of the 154 patients (10 from each of the two eras). There were no

TABLE 5. *Pseudocysts Found at Autopsy—Relationship to Death*

	1938-1961	1962-1974	Total
Pseudocysts as cause of death	6	2	8
Hemorrhage	3	1	4
Infection and Rupture	1	0	1
Infection	1	0	1
Pancreatitis	1	1	2
Pseudocysts not cause of death	2	3	5
Total	8	5	13

TABLE 6. *Results of Procedures for Pseudocysts in 154 Operative cases*

Years	Number of Patients		Recurrence		Mortality	
	1938-1961	1962-1974	1938-1961	1962-1974	1938-1961	1962-1974
Excision	10	10	0	0	1	1
External Drainage	37	26	15	3	2	5
Internal Drainage	9	62	0	3	0	6
Total	56	98	15	6	3	12
			26.8%	6.1%	5.4%	12.2%

recurrences. The mortality rate was 10%; 3 of the patients required additional operations for complications. One death occurred at operation from massive blood loss. A second death occurred in a patient who had severe chronic renal failure, respiratory failure, and a pleural effusion preoperatively. He died with sepsis, respiratory failure, empyema, and gastrointestinal bleeding. Four additional procedures were required in the three patients with complications. These included colon resection for bowel fistula in one, a vagotomy and pyloroplasty for gastrointestinal bleeding in one, and exploration to establish the resectability of pancreatic carcinoma in a patient whose pathology report postoperatively revealed carcinoma of the pancreas in the resected specimen.

Cyst-Gastrostomy

Cyst-gastrostomy was used in 36 patients with 2 recurrences. Four deaths resulted from complications as follow: One patient had severe cardiac and renal disease requiring hemodialysis preoperatively. Following his operation he developed pneumonia, empyema, respiratory failure, and progressive uremia. A tracheostomy was performed. He died of severe cardiac and respiratory disease. Another patient also had severe renal disease with a BUN of 140 and severe congestive heart failure. Follow-

TABLE 7. *Results of Internal Drainage Procedures for Pancreatic Pseudocysts*

Years	Number of Patients		Recurrence		Mortality	
	1938-1961	1962-1974	1938-1961	1962-1974	1938-1961	1962-1974
Cyst-Gastrostomy	2	34	0	2	0	4
Cyst-Jejunostomy	7	20	0	1	0	2
Cyst-Duodenostomy	0	8	0	0	0	0
Total	9	62	0	3	0	6

TABLE 8. *Complications After Pseudocyst Procedures*

Years	Complications		Additional Procedures Required	
	1938-1961	1962-1974	1938-1961	1962-1974
Excision	4/4*	3/7	1/1	2/3
External Drainage	15/28	15/20	15/20	5/5
Internal Drainage	3/8	18/37	2/2	8/12
Total	22/40	36/64	18/23	15/20
Per cent	39.3	36.8	32.2	15.3

*First number expressed is number of complications or procedures; second number expressed is number of patients.

ing operation he developed pneumonia, cardiac arrhythmias, and progressive renal decompensation ending in cardiac arrest. A third patient presented with jaundice, pneumonia, hypertensive encephalopathy (being unconscious on admission), and an infected pseudocyst. Postoperatively he was septic, his pneumonia progressed, he developed bilateral pulmonary edema and a pleural effusion, and he also required a tracheostomy. He died of respiratory failure and sepsis. The fourth patient died of massive bleeding. No definite source of bleeding was established and no autopsy was obtained.

Additional surgical procedures required for complications included the 2 tracheostomies mentioned above, 2 explorations for bleeding from the cyst cavity, and resection of a gastro-pancreatico-cutaneous fistula. One patient had an incisional hernioplasty performed on 2 occasions, and one patient had a laparotomy for a suspected recurrence of his cyst (which was not found).

Cyst-Jejunostomy

Cyst-jejunostomy was performed in 27 patients (17.5%). The only recurrence was in a patient who was lost to followup. Two deaths occurred in this group. The first patient died after his third episode of postoperative bleeding. The first episode was treated medically with success. He was readmitted three months later with a massive bleeding that required a hemigastrectomy. Two weeks after this he bled again, this time from his cyst. The bleeding point in his cyst was oversewn, but he died shortly after his operation. The other death in this group occurred in a patient who had severe chylous ascites thought to be secondary to retroperitoneal fibrosis with subsequent occlusion of lymph channels. This patient died of massive gastrointestinal bleeding three months after cyst-jejunostomy. Autopsy revealed thrombosis of the portal vein, esophageal varices, splenic vein thrombophlebitis, and a pulmonary embolus in addition to the above findings.

Complications occurred in 26% of the patients (Table 9). Additional operations were required for complications in 4 patients including the above patient who died. One patient had a negative exploration for a suspected intra-abdominal abscess. One patient had a gastrojejunostomy for pyloric obstruction secondary to scarring and inflammation caused by pancreatitis and pseudocyst compression. A fourth patient required exploration for bleeding from the cyst cavity.

Cyst-Duodenostomy

Cyst-duodenostomy was performed in 8 patients, all in Group II, with no recurrences and no deaths. There were

TABLE 9. *Postoperative Complications*

Complication	Number of Patients				
	External Drainage	Excision	Cyst Gastrostomy	Cyst Jejunostomy	Cyst Duodenostomy
Recurrence	18	0	2	1	0
Pancreatic fistula	6	1	2	0	1
Bleeding from cyst	4	1	1	2	0
Bleeding from GI tract	2	1	2	2	0
Bleeding unknown site	0	0	0	1	0
Sepsis	4	2	1	0	0
Respiratory complication	5	4	7	4	1
Bowel fistula	2	1	1	0	0
Wound dehiscence or infection	2	2	0	0	0
GU complication	2	0	3	0	0
Cardiac decompensation	1	0	2	0	0
Fully developed diabetes mellitus	1	0	2	2	0
Fully developed exocrine insufficiency	0	0	0	2	0
Pyloric obstruction	0	0	0	1	0
Retroperitoneal fibrosis and splenic vein thrombophlebitis	0	0	0	1	0
Intra-abdominal abscess suspected negative exploration	0	0	0	1	0
Persistent CBD obstruction	0	0	0	0	1

TABLE 10. *Mortality Corrected to Include All Pseudocysts*

	1938- 1961	1962- 1974	Total
Mortality attributable to cyst—Complications Deaths/Total patients	9/64	14/104	23/168
Per Cent	14.1	13.5	13.7

3 complications (Table 9) in 2 patients, and one patient required an additional procedure for a complication. One patient had a postoperative pancreatic fistula that closed spontaneously. One patient had atelectasis and required re-operation for persistent obstruction of the common bile duct.

Discussion

Pancreatic pseudocysts occur more commonly in males. Alcoholism and biliary tract disease are frequently associated, and penetrating or blunt trauma are not an infrequent cause of pseudocyst development. Symptoms of abdominal pain, nausea and vomiting, weight loss, and a perceived abdominal mass, and physical findings of tenderness and an abdominal mass are the hallmarks of the diagnosis particularly in any patient with a history of pancreatitis or possible pancreatic trauma. The most helpful diagnostic study was the upper gastrointestinal series with 83% of patients showing displacement of the stomach or duodenum. Plain films of the abdomen, cholangiography, arteriography, and ultrasound also may be used to establish the diagnosis in selected cases.

Jaundice was present in 16 patients and is an absolute indication for exploration. It was found to be progressive in nature and aided little by procrastination with medical management of accompanying pancreatitis.

Treatment should be expeditious but may await positive diagnosis and correction of associated problems. The untoward complications of infection, hemorrhage and rupture are associated with a high mortality rate (Table 4). These complications should be avoided by early intervention once the diagnosis is established and the patient adequately prepared. A major observation in the patients treated in the more recent era has been a reduction in the number of patients who have died without surgery (Table 5).

In this review we have identified a transition in the treatment of pancreatic pseudocysts. Two groups of patients were analyzed and compared—those treated before 1962 (Group I) and those treated beginning with 1962 (Group II). External drainage procedures as a method of therapy decreased from 66% in the earlier era to 27% in the more modern era. Internal drainage procedures and excision increased from 34% to 73%. The transition away

from external drainage procedures appears to be partially reflected by a reduction in recurrence rate. A decrease in the overall recurrence from 27% in Group I to 6% in Group II was seen. The overall recurrence rate for internal drainage was 4% and the rate for external drainage was 29%.

An analysis of complications reveals a 38% overall complication rate with no change in the modern era (39% in Group I, 37% in Group II). The overall complication rate for external drainage procedures was 48% and that for internal drainage was 30%.

Morbidity expressed as additional procedures required underwent a dramatic decline in the modern era. The overall rate for additional procedures was 21%; the rate for Group I was 32%, and the rate for Group II was reduced to 15%. This reduction in re-operation rate is partially explained by the decrease in recurrences. Thirty-two per cent of patients with external drainage procedures had additional operations performed, whereas only 14% of the patients with internal drainage procedures required additional operative procedures. This again reflects the high associated rate of recurrence with external drainage procedures.

Mortality in all patients was 14% for complications arising from the pseudocyst (Table 10). The operative mortality was 5% in Group I and rose to 12% in Group II. Examination of our data shows that a greater number of patients died of pseudocyst complications in Group I before an operation could be performed. In the more modern era, fewer patients died without an operation. This more aggressive surgical intervention is associated with a higher operative mortality rate in Group II patients, but overall mortality for all patients with pseudocysts has declined slightly in the modern era.

The literature emphasizes several points in the treatment of pseudocysts.^{1,2,5,6,8-11} Infected cysts should be drained externally. Small cysts, easily accessible, particularly if located in the distal pancreas may be excised. A well formed pseudocyst membrane is necessary for internal drainage. Close relationship to the duodenum or stomach and contiguous association to these organs is a prerequisite for anastomosis at these sites. A Roux-en-Y jejunal anastomosis can be used if the cyst is not attached to the duodenum or stomach, or if this is the more easily accomplished procedure, provided that the cyst is not infected and that it does not have a thin friable capsule. These criteria, although well established, are not always adhered to. In our series two cyst-gastrostomies were performed with a posterior cyst-gastric anastomosis. One of these resulted in 3 episodes of bleeding and a gastro-pancreatico-cutaneous fistula that required excision. Two infected pseudocysts were drained through the stomach. One of these resulted in death from associated complications.

The explanation for the dramatic transition away from

external drainage procedures appears to be related to an increasing awareness of the criteria for individualization of treatment. This trend is reflected in our data, but increasing adherence to established criteria will be necessary to achieve a further reduction in the morbidity, mortality, and recurrence rate in this disease.

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DISCUSSION

DR. CARLOS M. CHAVEZ (Jackson, Mississippi): Dr. Becker's group has had considerable experience in this type of problem which we have faced also from time to time.

(Slide) Our experience with 48 pancreatic pseudocysts at the University and Veterans Administration Hospitals has given us some experience in the management of this problem. Our method of choice, as Dr. Nance has pointed out, has been the cystogastrostomy, but several other methods have been used to drain this type of cyst. The technique we have adopted is the excision of a segment of the gastric or duodenal and the cystic wall, using interrupted sutures to control the bleeding.

Other procedures which have been associated with the internal drainage, or other type of drainage, have been the use of the cholecystectomy or the choledochoduodenostomy, and other incidental operations.

The complications have been quite interesting. The recurrence of the cyst following cystogastrostomy has been a little bit high for a series of 48 patients, and pancreatic ascites has been involved in some of these cases.

Bleeding has occurred in five patients, but in only one of them the bleeding was associated with lesions other than the pseudocyst.

I would like to bring up two interesting problems related to the presence of a mass, which has been diagnosed as pseudocysts, and at the time of exploration we found that the "pseudocyst" was not a true pseudocyst, but a pancreatic abscess or an abscess around the pancreas surrounded by omentum.

The other problem is that of the GI bleeding, pre or post drainage, and this is a real challenge for the surgeons, especially when the bleeding comes from the cystic cavity.

I would like to ask Dr. Nance if he has run across these problems, and what was the way he managed them.

DR. R. SCOTT JONES (Durham, North Carolina): The points I wish to make relate to the use of diagnostic ultrasound in evaluation of patients with masses believed to be in the pancreas.

With the aid of our Radiology Department, we have been using this method with increasing frequency and confidence, and have found it very helpful in discriminating between the patients who have a large inflammatory mass and those who have a pseudocyst.

(Slide) These are some ultrasounds done on a young woman involved in an automobile accident. At day 4 after the injury there is the appearance of what was an early cystic cavity. Four days later it is somewhat larger and somewhat better defined. And then four days later, or twelve

days after the accident, these studies revealed a fairly well-defined pseudocyst.

(Slide) This is a case of a young man who had acute pancreatitis. Initially when he was studied there was no good evidence of a cyst. Incidentally, he had an abdominal mass. Approximately a week later the ultrasound study was beginning to show evidence of pseudocyst formation, and then subsequently, one week later, there was a fairly well-defined, fluid-filled space. This is a lateral examination.

We feel that the ultrasound method is very helpful in evaluating the patient who has an abdominal mass, tenderness, and elevated amylase, after trauma or an episode of pancreatitis, and feel that it will aid materially in the judgments about these patients.

DR. PAUL R. HASTINGS (Closing discussion): Dr. Chavez and Dr. Bunch have both brought up the problem of bleeding. As was pointed out, we had numerous problems with bleeding preoperatively as well as postoperatively. When a patient is bleeding preoperatively, he may be bleeding from a number of sites. You would think automatically he would be bleeding into the cyst, but there were a number of patients who had stress bleeding from ulcers associated with pancreatic disease.

In regard to the question about the pseudocyst versus an abscess, when you do find an abscess, or an infected pseudocyst, you must drain it. Anastomosis to an internal organ usually does not stand up well.

As far as the question of Dr. Jones—he brought up ultrasound. We think that ultrasound is a very good method of differentiating pseudocysts. We have used ultrasound in only two patients, and those were in the very last few months. It was indicative of a nonsolid mass in both patients.

I would like to bring up just two more points. One is jaundice. There were 16 patients in our series who had jaundice preoperatively. In two of these the jaundice was due to an associated carcinoma of the pancreas. In 14 it was due to compression of the common bile duct. A few of these patients were observed and treated clinically. Their bilirubin did drop. We feel that the presence of jaundice is an absolute indication for very early surgical intervention.

Finally, we feel that our data show a healthy trend toward the right direction of relying on individualization in the treatment of this disease. We feel we have shown a good reduction in the recurrence rate, and a good reduction in the morbidity (expressed as additional procedures required).

We also feel that if more individualization had been done, several complications would have been avoided, and the mortality and complication rate would have also been decreased.

Conservative Surgical Treatment of Reflux Esophagitis and Esophageal Stricture

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During a recent 3-year period, 17 consecutive patients were seen with advanced fibrotic esophageal strictures secondary to alkaline-acid-pepsin reflux. From detailed preoperative evaluations alone it was impossible to determine whether therapy should consist of excisional surgery, esophagogastroplasty or intraoperative dilatation with correction of reflux. Only at operation could the length, extent, degree and severity of the stricture be fully determined. Each of the 17 patients was treated by controlled dilatation, coupled with an antireflux procedure. This simplified approach proved successful on strictures thought preoperatively to be undilatable. It appears that this conservative approach is applicable to many advanced strictures and excisional and plastic procedures should be reserved for those cases that prove unyielding to intraoperative dilatation. The true appraisal of a reflux stricture and the choice of surgical procedure is best determined at the operating table.

THE DEVELOPMENT of an esophageal stricture secondary to reflux esophagitis is usually the result of failure of medical treatment or patient neglect and may be preventable. It is an unpredictable phenomenon and may present either early or late in the symptomatic patient. The stricture may be short and annular or longitudinal and ascending. In the former the inflammatory reaction is usually confined to the esophageal mucosa and submucosa, and the stricture is located at or near the gastroesophageal junction. In the latter there is usually extensive transmural involvement which may spread to the periesophageal and mediastinal structures. Such strictures may extend proximally to the level of the aortic arch, and the esophagus below the stricture may or may not be lined with columnar epithelium.^{1,17,18}

Controversy continues to exist regarding the surgical management of the reflux stricture and a wide range of operative procedures has been suggested. Some authorities feel that operations of considerable magnitude as esophageal resection with jejunal or colonic interposi-

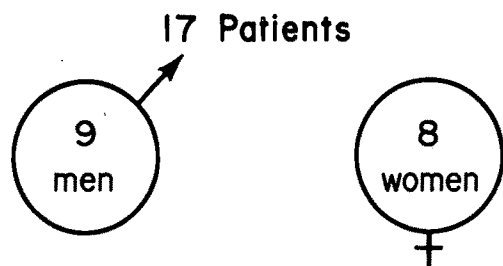
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tion or esophagogastroplasties of the Thal-Nissen, Collis, or Heimlich types are necessary to achieve success. Valvular esophagogastrostomy and stricture excision combined with vagotomy-antrectomy with either Roux-en-Y diversion or Henley loop construction have been employed. Transgastric excision of annular strictures combined with an antireflux procedure has also been reported with good results.^{1,8,9,11,14,19,23,25,30,38,41,43}

The preoperative assessment of an esophageal stricture using barium swallow, cinéfluoroscopy, endoscopy with biopsy, and attempts at dilatation may at times be misleading. Actual stricture length and degree of esophageal fixation and fibrosis may not always be accurately determined by such studies. Therefore to choose a particular surgical procedure on the basis of such clinical information would appear unsound. Hayward^{12,13} of Australia was perhaps the first to emphasize that selection of operation should be made at the time of surgery after the extent and degree of the stricture have been thoroughly ascertained. Operative findings correlated poorly with preoperative evaluation in his experience. Hayward found that many tough, fibrous strictures in patients with persistent dysphagia could be treated by operative dilatation accompanied by an antireflux procedure, and seldom was resectional surgery necessary.

In this country Hill^{15,16} has pursued the simplified approach and has convincingly shown that advanced strictures respond to this method of therapy. Moran²¹ likewise stresses that the exact extent and degree of an esophageal stricture can only be determined at operation and many advanced strictures of long standing can be successfully

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Age Range: 46 — 90 yrs

Average Age: 63 yrs

DURATION OF SYMPTOMS: 18 mos — 30 yrs

FIG. 1. Reflux Esophageal Stricture.

dilated intraoperatively and a satisfactory result obtained if associated reflux is corrected. Brindley,⁴ Paulson^{23,24} and Boyd³ have each noted satisfactory results with this method.

The purpose of this communication is to cite a recent three-year experience in which this conservative surgical approach was used in the management of a small group of 17 consecutive patients with advanced reflux stricture.

Material

There were 9 men and 8 women among the group of 17 patients comprising the clinical study. The ages ranged from 46 to 90 years with the average age being 63 years. Symptoms suggesting reflux esophagitis were present from 18 months up to 30 years. Two patients had undergone unsuccessful surgical attempts for correction of gastroesophageal reflux (Fig. 1).

Severe and persistent dysphagia was experienced by each patient. Eight patients had complete or near complete obstruction to liquid intake, and three patients had difficulty swallowing their saliva. The remaining patients could not partake of solid food.

The preoperative workup included barium examination of the esophagus and upper gastrointestinal tract when possible, cinefluoroscopy, and esophagoscopy with biopsy. The presence of carcinoma was ruled out in each of the cases. Barium enema examination was done to assess colonic length and to exclude colonic disease should a colon interposition procedure prove necessary. In 10 cases the stricture was of the longitudinal type, and in 7 cases a short distal annular stricture existed (Fig. 2). In some of the latter cases preoperative dilatation was attempted but proved unsuccessful. Dilatation was primarily carried out as an integral part of the operative procedure in all cases.

Method

The conservative approach to the treatment of reflux stricture may not be applicable to all cases; therefore preoperative discussions with the patient, the operating team, and nursing personnel give consideration to the possible performance of a more radical procedure should the stricture prove unyielding to intra-operative dilatation.

The abdomen is first opened and after general exploration attention is directed to the left upper abdominal quadrant. The suspensory ligament of the left hepatic lobe is divided and the lobe retracted to the right. The peritoneal and fibrous structures about the proximal stomach and distal esophagus are freed next. The cephalad portion of the gastrohepatic omentum is transected, and the greater gastric curve mobilized by dividing the uppermost vasa brevia vessels. If the stricture is of the longitudinal type or the annular variety that proved unyielding on preoperative assessment, a short transverse gastrotomy is performed on the anterior wall of the cardia just below the gastroesophageal junction and held open with Guy sutures. The gastroesophageal orifice is visualized and palpated digitally to determine the degree of stenosis present. With the fingers of the surgeon's left hand placed behind and around the proximal cardia and distal esophagus, the stenosed gastroesophageal aperture is gently dilated with graduated Hegar dilators.

Simultaneously, a member of the operating team passes a rigid gastroscope *via* the oral route to the proximal limit of the stricture. Graded filiform dilators are then passed through the stricture followed by tapered Maloney dilators. A number 20F is used initially followed by graduated sizes up to a number 34 to 38F. The rigid gastroscope is removed as the larger Maloney dilators are

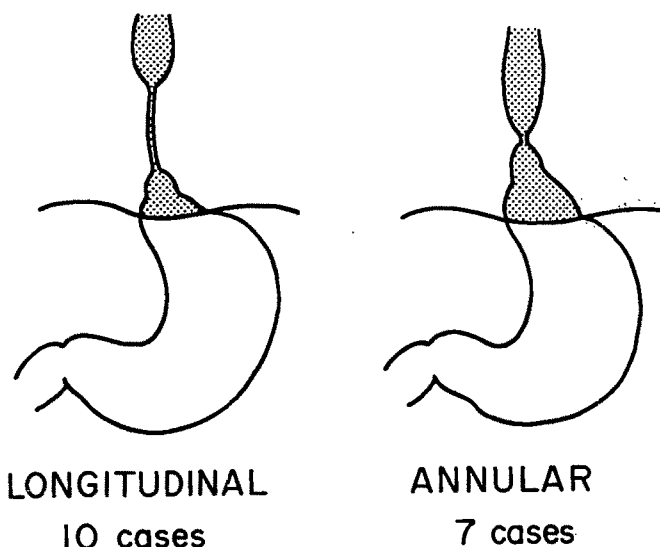


FIG. 2. Types of esophageal strictures encountered among the 17 patients.

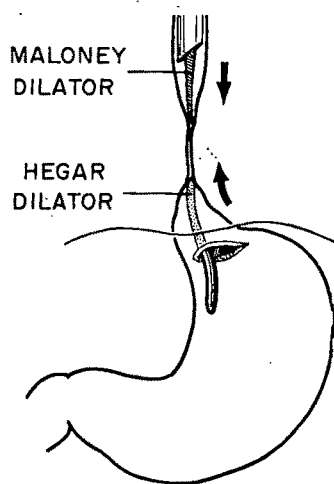


FIG. 3. Sketch depicting simultaneous antegrade and retrograde dilatation of a longitudinal esophageal stricture.

introduced. During this time the operator continues to dilate the distal limits of the stricture *via* the gastrostomy and the tapered dilators introduced from above will be seen to pass gradually through the length of the stricture. With the stricture now open larger Maloney dilators may be safely passed from above while the operator clearly visualizes the interior of the distal esophagus. With the left hand positioned around the esophagus he can determine the extent to pursue the dilatations from above (Fig. 3).

After satisfactory dilatation the gastrotomy is closed and the attenuated defect in the right crural sling is approximated if the gastroesophageal junction lies below the diaphragm without tension. Should it prove difficult or impossible to bring the gastroesophageal junction below the diaphragmatic level, it is best to leave the crural aperture unapproximated with a small portion of gastric cardia displaced in the posterior mediastinum. In two of the present cases a small portion of the cardia was left above the level of the diaphragm. In two other cases the crural defect was small and the muscle fibers were purposely not approximated. Each of the 17 patients was found to have a sliding esophageal hiatal hernia. As the final important step an antireflux procedure is carried out. Fifteen patients underwent a Nissen fundoplication operation, one had a Hill posterior gastropexy, and a Belsey repair was used in one patient (Fig. 4).

Two patients had an associated duodenal ulcer, and vagotomy and pyloroplasty were done. Eight patients among the group required simultaneous antegrade and retrograde intraoperative dilatation, whereas 9 patients underwent antegrade dilatation only.

Illustrative Cases

Case 1 M.H.: A 46-year-old woman was admitted to St. Thomas Hospital 3/20/74 with a 10-year history of upper abdominal discomfort, frequent eructations and substernal burning. Four months before admission she had been evaluated elsewhere and was told that she had a

small sliding esophageal hiatus hernia with gastroesophageal reflux. Esophagoscopy at the time showed evidence of esophagitis, but there was no stricture formation. She was treated with a bland diet, antacids and told to sleep with the head of her bed elevated. The patient followed these instructions for a few weeks, but did not improve and therefore discontinued medications as well as her physician's advice. During the next several weeks she noted progressive dysphagia and lost 30 pounds in weight. She experienced no melena or hematemesis.

When seen at our institution a barium swallow revealed a stricture of the lower esophagus and the barium pill failed to progress through the strictured area. Endoscopy showed a localized annular stricture 36 cm from the incisor teeth, and mucosal biopsy revealed no evidence of malignancy. Only the smallest Maloney tapered dilator (20F) could be passed through the strictured area with difficulty.

At operation the gastroesophageal junction was freed up and a small sliding esophageal hiatal hernia was present. Esophageal dilatation was carried out *via* the oral route by a member of the operating team using graduated Maloney dilators, beginning with a 20F and gradually increasing to a 40F. During manipulation from above, the operator from below, with the fingers of his left hand around the distal esophagus, guided the graduated Maloney dilators through the stricture. The small defect in the right crural sling was repaired followed by a Nissen fundoplication.

During a 9 month followup the patient has remained asymptomatic. She has regained her lost weight, and postoperative esophageal dilatation has not been necessary. Several repeat barium swallows during this time reveal the lower esophagus to be essentially normal (Fig. 5). Endoscopy likewise reveals normal findings.

Comment. Although this patient had been experiencing symptoms of gastroesophageal reflux for a number of years, she developed the annular stricture over a relatively short period of several weeks. It was not necessary to dilate the stricture through a gastrotomy incision as controlled dilatation by a member of the operating team

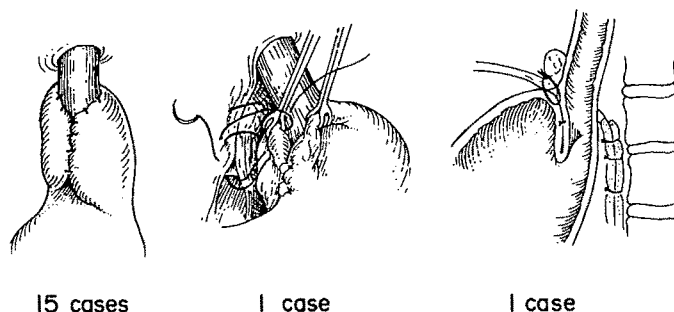


FIG. 4. Types of antireflux procedures performed among the 17 patients.

FIG. 5A. Case 1: Preoperative esophagram showing a distal annular esophageal stricture with the barium pill trapped just above the strictured area.



working from above in conjunction with guidance from below proved successful.

Case 2—J.F. A 62-year-old Negro man was admitted to St. Thomas Hospital 11/6/73 with a 12 year history of burning epigastric pain, relieved somewhat by the intake of food, along with substernal distress and frequent regurgitation. During the past year he noted progressive symptoms of dysphagia and currently was unable to swallow solid food. Barium studies revealed a striking longitudinal narrowing of the distal esophagus and the presence of a moderate size sliding esophageal hiatus hernia. There was also a pronounced deformity of the distal pylorus and duodenal bulb consistent with the diagnosis of channel ulcer (Fig. 6). Esophagoscopy demonstrated marked narrowing of the esophagus above the level of the

hiatus hernia and no evidence of malignancy was present. Preoperative esophageal dilatation was not performed.

At laparotomy a moderate size sliding esophageal hiatus hernia existed. It was elected to first attempt dilatation of the esophageal stricture from above by a member of the operating team. The 20F tapered Maloney dilator was passed through the stricture and after careful and meticulous manipulations additional graduated dilators up to a 38F were passed. The defect in the crural sling was approximated as the gastroesophageal junction could be brought below the diaphragmatic level without tension. A Nissen fundoplication was carried out and the gastroesophageal orifice was calibrated over a No. 38 Maloney dilator. The dilator was then removed and a nasogastric tube was passed into the stomach. A bilateral truncal vagotomy and Weinberg type pyloroplasty were performed for the channel ulcer (Fig. 7).

Following the antireflux procedure the patient was relieved of dysphagia and after a one year follow-up has no

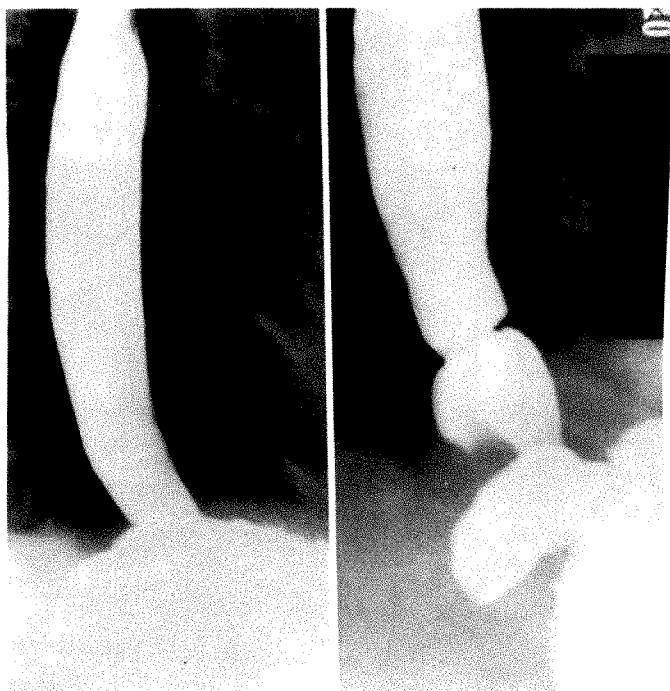


FIG. 5B. Postoperative barium study showing complete correction of the stricture. The deformity at the gastroesophageal junction depicts the Nissen fundoplication.



FIG. 6. Case 2: Preoperative barium esophagogastrintestinal study depicting a tight, longitudinal esophageal stricture with a moderate size sliding esophageal hiatus hernia. Also a rather marked deformity of the distal pyloric channel and duodenal bulb exist.

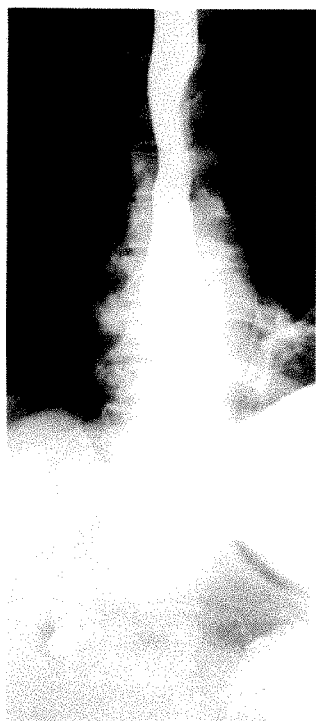


FIG. 7. Case 2: Upper gastrointestinal study in the early postoperative period shows correction of the esophageal stricture and hiatus hernia. The gastroesophageal junction has been calibrated over a No. 38 Maloney dilator and an antireflux operation performed.

symptoms referable to the gastro-intestinal tract. A recent barium study of the esophagus and stomach reveals only slight narrowing at the area of the previous stricture and endoscopic examination shows no evidence of esophagitis. The ulceration in the duodenum remains healed (Fig. 8).

Comment. Although this patient had a tight longitudinal stricture above the sliding esophageal hiatal hernia it was possible to dilate the stricture adequately from above and retrograde dilatation through a gastrotomy was not necessary.

Case 3—H.N. A 55-year-old man entered St. Thomas Hospital 4/5/73 with the complaint of severe dysphagia. For several months he had not been able to partake of solid foods. Five years prior he had undergone an Allison repair for a sliding esophageal hiatus hernia. The patient was relieved of symptoms until approximately one year prior to the present admission when he experienced difficulty swallowing. There had been a 15 pound weight loss. Esophagram revealed an advanced distal longitudinal stricture along with a recurrent hiatus hernia. Esophagoscopy showed the presence of the stricture and a biopsy demonstrated no evidence of malignancy. Preoperative attempt at esophageal dilatation performed elsewhere was unsuccessful. Further dilatation was not pursued at our institution.

At operation the recurrent hiatal hernia was reduced with some difficulty, and through an anterior gastrotomy, the gastroesophageal junction, which was extremely stenosed, was dilated with graduated Hegar dilators. Simultaneously, a member of the operative team from above dilated the proximal aspect of the stricture, employing graduated filiform dilators passed through the rigid gastroscope. The scope was withdrawn and graduated tapered Maloney dilators, up to a 38F, were introduced through the stricture. A No. 15 Hegar dilator was finally passed retrogradely, thus opening the entire strictured area. The crural sling was next approximated and a Nissen fundoplication was performed over a 38F Maloney dilator.

The patient has now been followed 20 months, has gained 30 pounds and experiences no difficulty swallowing. A recent barium study of the upper gastrointestinal tract reveals no evidence of reflux and the diameter of the distal esophagus is within normal limits (Fig. 9).

Comment. Combined antegrade and retrograde dilata-

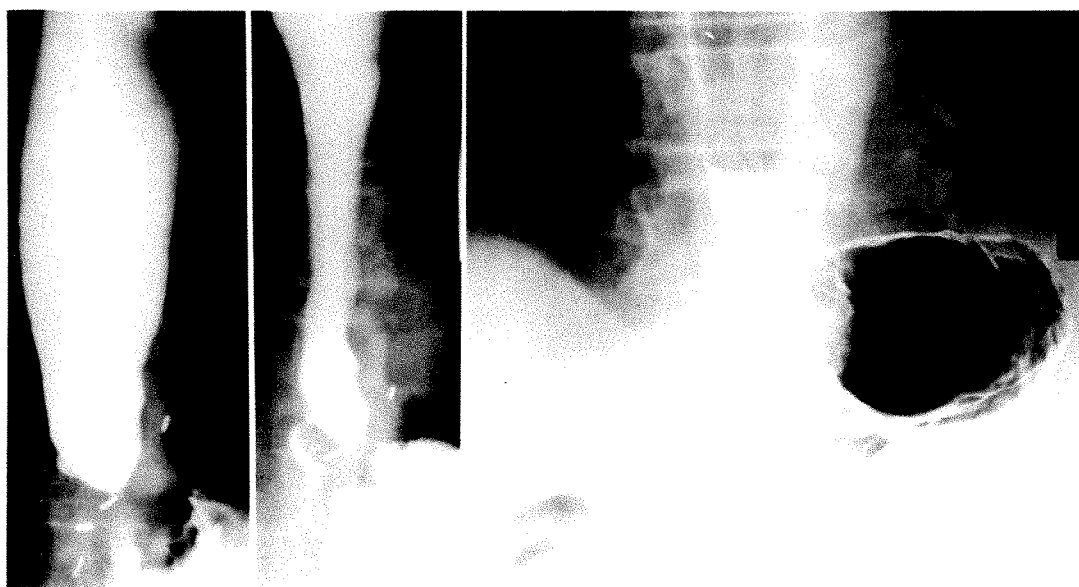
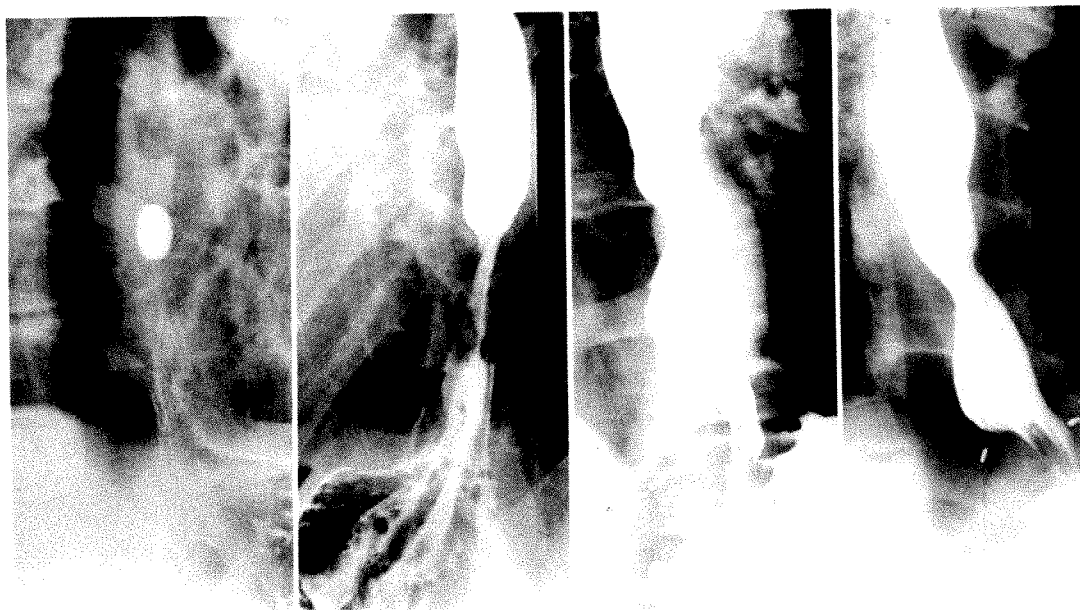


FIG. 8. Case 2: Barium study one year postoperative reveals no evidence of recurrent stricture or hernia formation. The patient has been relieved of all symptoms.

FIG. 9. Case 3: (Left) Barium swallow showing the advanced, longitudinal stricture with associated hiatus hernia. (Right) Upper gastrointestinal barium study 20 months postoperative reveals no evidence of recurrent stricture formation and no hiatus hernia.



tion of the strictured esophagus proved necessary in this case. In our opinion neither approach alone would have sufficed in alleviating the esophageal stenosis. Preparations had been made prior to operation to perform a more radical procedure such as colon interposition had combined efforts at dilatation been unsuccessful.

Case 4—M.P. A 68-year-old woman was admitted to St. Thomas Hospital 10/1/73 with a one year history of progressive difficulty in swallowing. Within recent months

she was only able to swallow liquids and experienced a 20 pound weight loss. She had noted heartburn and epigastric fullness over the past 12 years, and 5 years before admission an upper gastrointestinal study revealed the presence of a sliding esophageal hiatal hernia. Aside from the occasional use of Donnatal and Valium she had had no specific treatment.

Barium swallow revealed a striking, tapering stenosis of the distal esophagus with the lumen measuring 2 mm, at its narrowest point. Distal to the stenosed area a fine trickle of barium outlined a small hiatus hernia (Fig. 10). Esophageal biopsy showed no evidence of tumor.

At operation, through a midline abdominal incision, a high gastrotomy opening was made and retrograde dilatation of the stricture was carried out using graduated Hegar dilators. Simultaneously, the stricture was dilated from above using filiform dilators followed by graduated tapered Maloney bougies. The esophagogastric junction was brought below the diaphragmatic level without tension, and the right crural sling was approximated. A Nissen fundoplication was performed over a 36F Maloney dilator.

The patient has been carefully followed for 14 months and has not required subsequent dilatation. Symptoms have been relieved and a recent barium study of the upper gastrointestinal tract reveals the esophagus to be entirely normal (Fig. 11).

Comment. This patient presented with an extremely tight and fibrotic stricture of the distal esophagus which was longitudinal in type. From a study of the preoperative esophagram some doubt was raised as to whether this stricture could be dilated intraoperatively. However, using the combined approach adequate dilatation was performed, followed by an antireflux procedure.

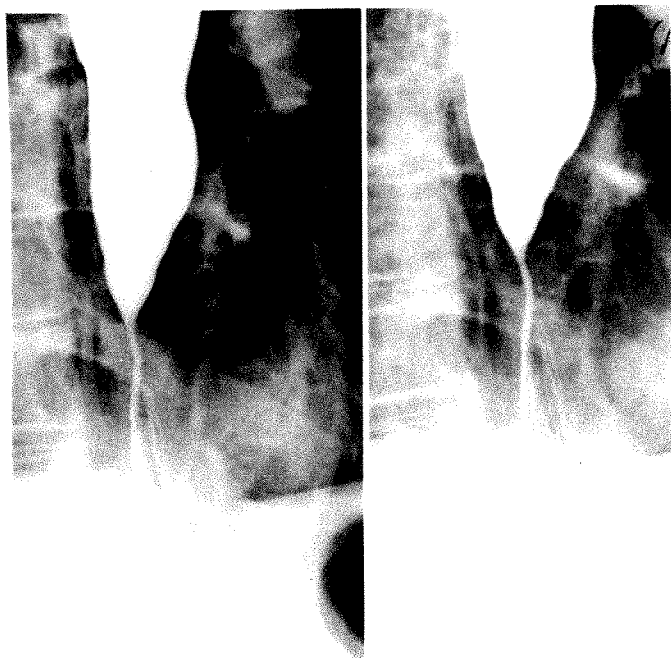


FIG. 10. Case 4: Preoperative barium swallow demonstrating a tapering stenosis of the distal esophagus with an esophageal lumen measuring 2 mm.

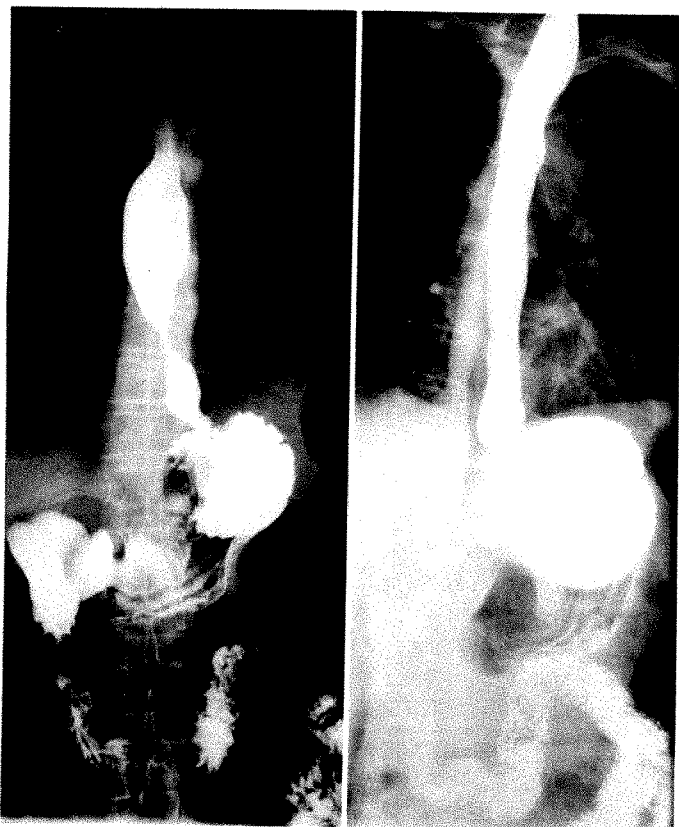


FIG. 11. Case 4: (Left) Barium swallow on the 7th postoperative day reveals some increase in the diameter of the esophageal lumen as compared to the preoperative study. (Right) Upper gastrointestinal contrast study 14 months postoperative reveals the esophagus and esophagogastric junction to be perfectly normal. The patient was relieved of all symptoms during the early postoperative period and did not require additional dilatation.

Case 5—A.H. A 49-year-old man was admitted to St. Thomas Hospital 6/25/74 with a 3 year history of upper abdominal discomfort, substernal burning and frequent regurgitation. He had been diagnosed elsewhere as having a sliding esophageal hiatus hernia and appropriate medical treatment was instituted. However, symptoms progressed in severity and he began to experience dysphagia. He could not swallow solids and it was necessary for his wife to puree his food.

Barium study revealed a tight, annular, distal esophageal stricture and just below the stricture was a moderate size sliding esophageal hiatus hernia (Fig. 12). Biopsy ruled out the presence of carcinoma and all other findings were normal.

Through an abdominal approach the esophageal hiatal hernia was freed up and the distal esophagus exposed. With the fingers of the operator's left hand surrounding the esophagus, a member of the operating team from above passed the graded Maloney dilators through the stricture site beginning with a No. 20F and progressing to a 44F. A Nissen fundoplication was then performed over a No. 38F Maloney dilator and the crural sling was pur-

posely not reapproximated. The operator was unable to displace the lower few centimeters of the esophagus below the diaphragm without producing tension on the former structure. Therefore a portion of the fundoplication was left above the diaphragmatic level, and the edge of the diaphragm was sutured loosely to the mid aspect of the fundoplication.

Postoperatively the patient did well but necessitated dilatation on two occasions for mild upper abdominal discomfort. Esophagoscopy shows no evidence of reflux or esophagitis and a barium swallow 6 months postop revealed improvement over the early postoperative study with only slight narrowing at the former stricture site. The esophageal lumen, however, appears adequate. The Nissen fundoplication may be seen lying partially in the posterior mediastinum and it functions adequately in preventing reflux (Fig. 13).

Comment. This annular stricture could undoubtedly have been adequately excised through a transgastric approach. However, dilatations from above proved adequate and obviated the need for anterior gastrotomy. Some, perhaps, might have elected to treat this stricture by the more complicated method of Thal.

Case 6—U.B. A 68-year-old woman was admitted to the Metropolitan General Hospital 10/10/71 with a 30 pound weight loss and progressive dysphagia over a period of 6 months. Recently she had experienced difficulty in swallowing liquids. Past history showed that for at least 10

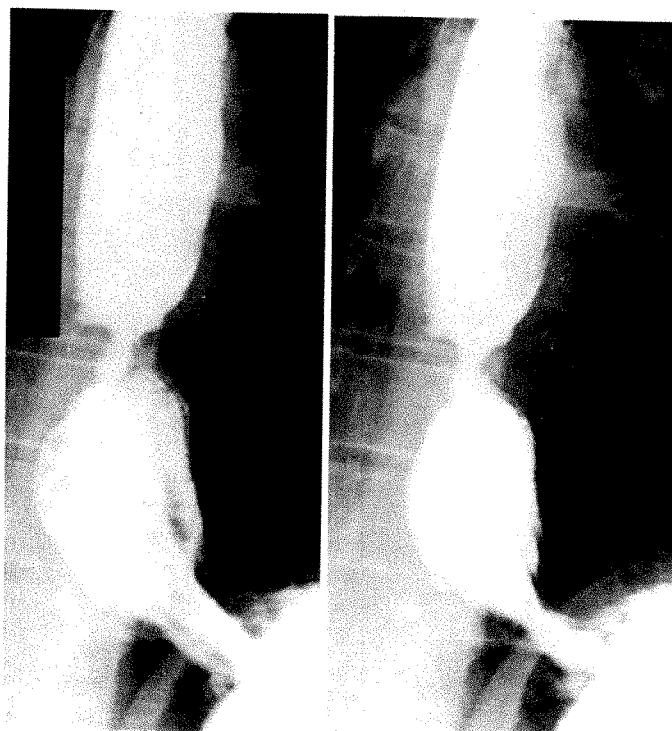
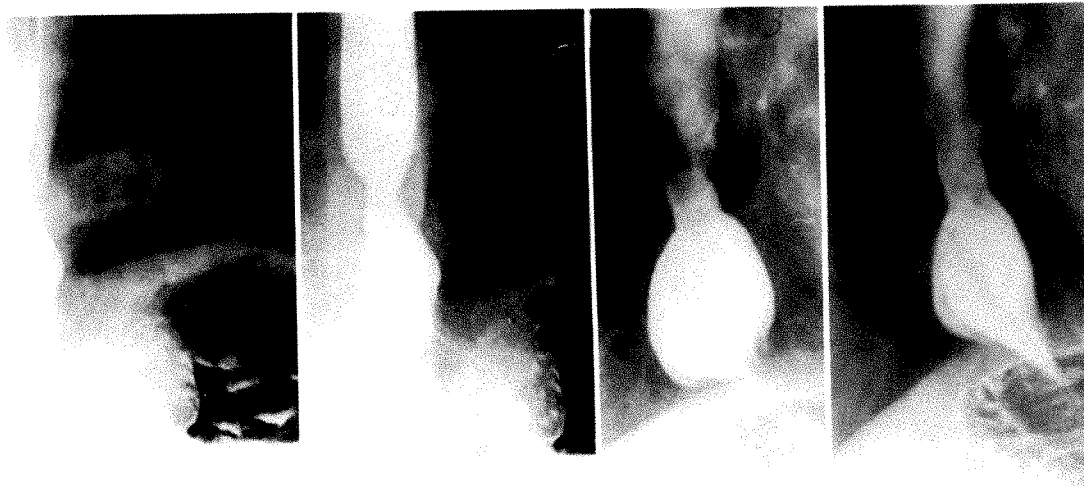


FIG. 12. Case 5: Preoperative barium study shows a tight, annular, distal esophageal stricture with a sliding esophageal hiatus hernia.

FIG. 13. Case 5: Barium study 6 months postoperative reveals only slight narrowing at the former stricture site. The Nissen fundoplication may be seen lying partially in the posterior mediastinum. This patient required dilatation on two occasions during the early postoperative period, after which he has been relieved of all symptoms.



years she had noted heartburn, upper abdominal fullness and substernal distress. A hiatus hernia was diagnosed at that time but the patient had not followed medical therapy.

Barium examination of the esophagus revealed a tight, longitudinal stricture, and distal to the narrow barium column a small hiatus hernia was visualized (Fig. 14). Biopsy taken from the proximal limit of the stricture showed no evidence of malignancy and preoperative dilatation was not attempted.

At operation, employing a left thoracotomy, the longitudinal stricture was dilated from above while the operator controlled the dilatations with his fingers about the mobilized esophagus. A Belsey Mark IV antireflux procedure was then carried out. The patient required several dilatations during the first few post-operative

months and the stricture was gradually dilated up to a Maloney 44F.

An upper gastrointestinal study 3 years postoperative revealed the esophagus to be normal (Fig. 15). No reflux can be demonstrated on endoscopy and no recurrent hiatus hernia is noted. The patient does experience mild to moderate upper abdominal burning pain which is controlled with medications.

Comment. This case represents a tight, longitudinal stricture of the distal one-third of the esophagus which some surgeons prefer to treat by an interposition procedure or esophagogastroplasty. A less formidable procedure, however, sufficed to alleviate this patient's dysphagia completely.

Case 7—J.R. A 69-year-old Negro man was admitted to St. Thomas Hospital 10/5/72 with a 30 year history of

FIG. 14. Case 6: Preoperative esophagram showing an advanced, longitudinal stricture of the lower esophagus.

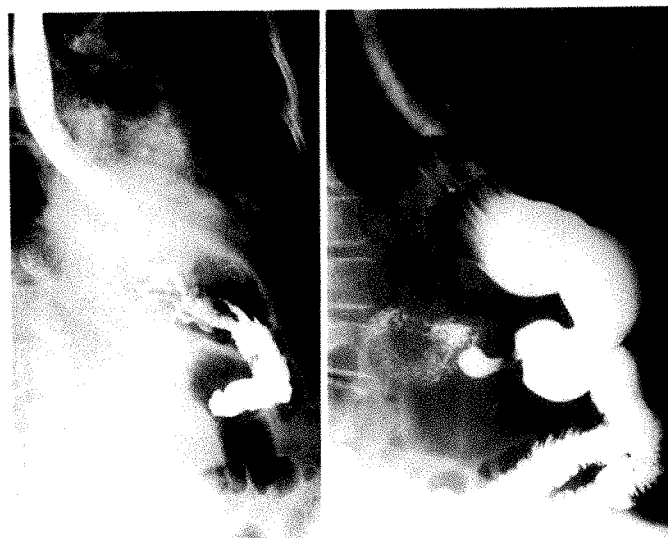
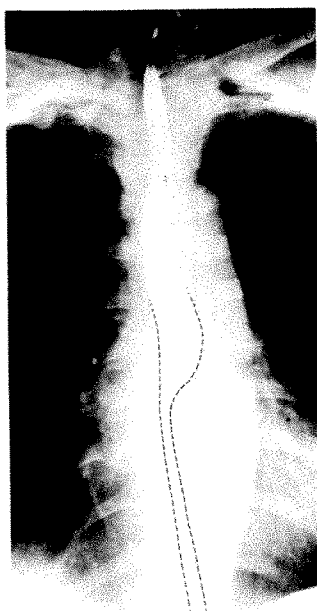


FIG. 15. Case 6: Gastrointestinal study 3 years postoperative reveals the caliber of the esophageal lumen to be normal. The Belsey Mark IV antireflux procedure continues to function adequately.



FIG. 16. Case 7: Barium study showing a far-advanced longitudinal stricture with dilatation of the esophagus proximal to the stricture.

upper abdominal fullness and substernal discomfort. For the past 12 weeks before admission he experienced progressive dysphagia and had difficulty swallowing liquids. He had lost 40 pounds in weight and experienced marked lassitude and fatigue.

Upon admission the patient appeared acute and chronically ill and showed evidence of marked weight loss. He had difficulty swallowing his saliva. The hemogram was 10, albumin was 2.2 and total serum protein was 5.8. Extensive workup was done including an upper gastrointestinal study which showed dilatation of the proximal esophagus, and beginning 33 cm, from the incisor teeth there was an advanced fibrous stricture (Fig. 16). However, after several minutes of fluoroscopic observation, a trickle of barium was seen to pass through the strictured area. At endoscopy the proximal limit of the stricture was visualized and a biopsy showed no evidence of tumor. A No. 4 filiform catheter could not be introduced through the stricture. The patient was given adequate blood and colloid replacement and put on total parenteral hyperalimentation for a period of 3 weeks. During this time he gained 15 pounds and his general condition improved considerably.

At operation the stricture was dilated retrogradely via

anterior gastrotomy with graded Hegar dilators and from above by first employing filiform catheters, followed by graduated tapered Maloney dilators up to a No. 34F. The crural sling was approximated and a posterior gastropexy as described by Hill was used to correct reflux.

Postoperatively the patient did well and was able to progress to soft food. Dilatations were continued for several months and he was able to eat a soft diet but certain foods were poorly tolerated. Adequate nutrition was maintained and the patient was satisfied with the clinical result. An x-ray 18 months after operation showed mild dilatation proximal to the original stricture but the stenosed area had opened up considerably and an ample lumen was present (Fig. 17). The patient was followed for a period of two and one half years at which time he died of a cerebrovascular accident.

Comment. This elderly gentleman presented with a far-advanced fibrotic longitudinal stricture and preoperative opinions from several authoritative consultants were that a radical approach to the stricture would be necessary. However, combined dilatation from above and below along with the antireflux procedure produced an acceptable result.

Case 8—V.B. A 53-year-old woman was admitted to Metropolitan City Hospital 5/25/72 with a 6 year history of upper abdominal fullness, heartburn and regurgitation.

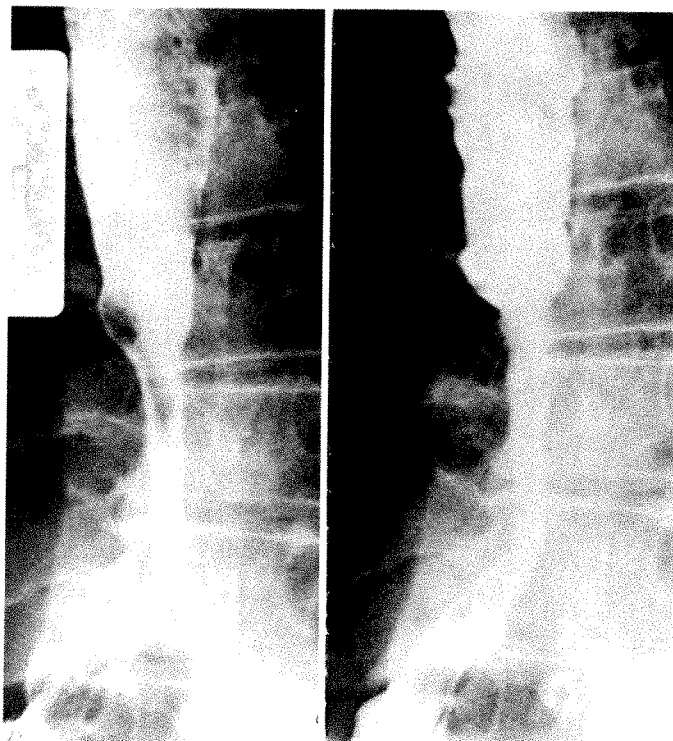


FIG. 17. Case 7: Contrast study of the esophagus 18 months postoperative reveals minimal dilatation of the proximal esophagus, but the lumen through the previous strictured area appears adequate. Esophageal dilations were necessary for several months postoperative, but this elderly patient was able to eat a soft diet without difficulty.



FIG. 18. Case 8: Preoperative barium swallow shows marked dilatation of the proximal esophagus with retained food and secretions. Distal to the dilatation a striking longitudinal esophageal stricture is present. This patient had difficulty swallowing her saliva.

During the past year she had experienced difficulty in swallowing and currently was only able to partake of a liquid diet.

An esophagram revealed the proximal esophagus to be

markedly dilated with evidence of retained fluid. No peristaltic activity was present and esophageal emptying took place by increased hydrostatic pressure with the patient erect. Distal to the dilatation an advanced longitudinal stricture was noted (Fig. 18). Esophagoscopy confirmed the diagnosis of a pronounced esophageal stricture and biopsy at the proximal limit of the stricture showed no evidence of malignancy.

After adequate preoperative preparation the stricture was dilated using the combined approach followed by a Nissen fundoplication. Several dilatations were instituted for a few weeks postoperatively after which they were discontinued. During the ensuing months the patient gained 47 pounds and a barium swallow showed marked improvement. She has been seen at frequent intervals during the past two and one half years, has no dietary limitations, and is symptom-free. A recent esophagram reveals a slight narrow area in the distal esophagus but the lumen through this area measures almost one cm. (Fig. 19).

Comment. This patient also presented with an advanced fibrotic stricture and one could not determine from preoperative assessment whether intraoperative dilatation would be possible. However, intraoperative combined dilatations followed by an anti-reflux operation proved effective in eliminating symptoms and restoring the esophagus to near normal. Although slight narrowing of a segment of esophagus exists, it has caused the patient no symptoms over a two and one half year followup.

Case No. 9—L.R. A 90-year-old Caucasian man was admitted to St. Thomas Hospital 10/3/71 with a history of dyspepsia dating back at least 40 years. He had been told that he had an esophageal hiatal hernia, but had never

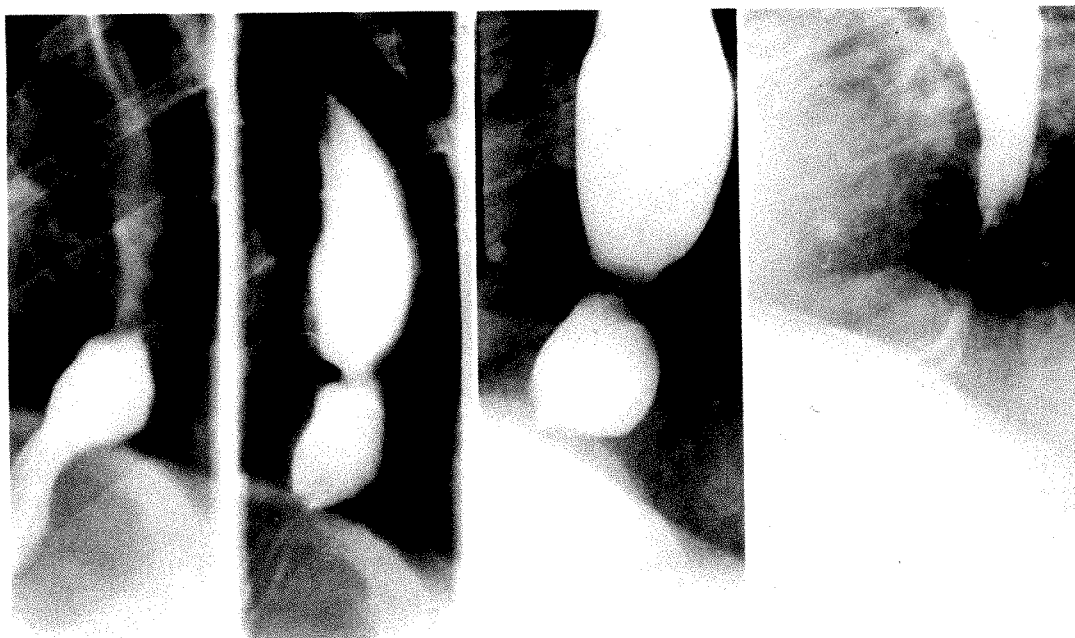


FIG. 19. Case 8: (Left) An esophagram during the early postoperative period after 2 dilatations reveals only slight narrowing with correction of the longitudinal stricture. (Right) An esophagram 2 years post-operative reveals only slight esophageal narrowing and the patient has obtained an excellent result.

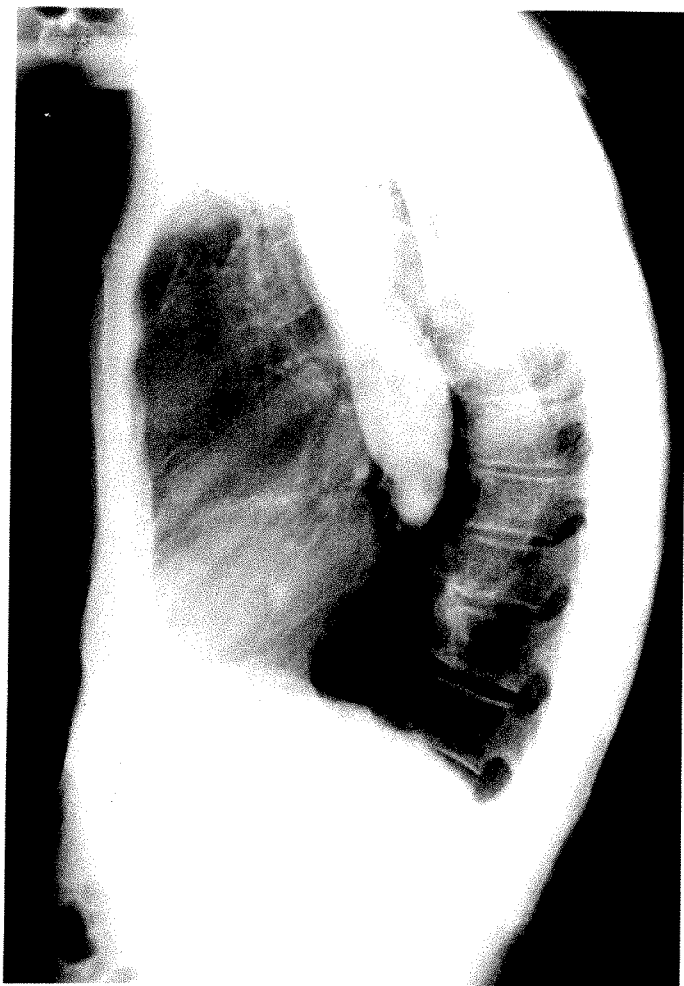


FIG. 20. Case 9: Complete esophageal obstruction resulting from benign reflux stricture. This 90-year-old patient could not swallow liquids and had difficulty swallowing his saliva.

been advised to follow a medical program. Eight years before admission he underwent a cholecystectomy and during the postoperative course a nasogastric tube was kept in place for several days. Following discharge from the hospital dyspepsia increased and he experienced rather severe substernal distress and regurgitation. He noted progressive difficulty swallowing solid foods and for the next several years consumed a soft diet. Several months before admission he noted difficulty swallowing liquids and for a few weeks prior to admission had difficulty swallowing his saliva. He lost about 40 pounds during this period and experienced marked weakness and fatigue.

Upon admission the patient appeared chronically ill and the hemogram was 9.4. A barium swallow revealed marked dilatation of the proximal esophagus and complete obstruction was noted at the junction of the middle and distal third (Fig. 20). Esophagoscopy confirmed the presence of complete obstruction but no evidence of a tumor was noted. After an extensive workup and

preoperative preparation with total parenteral nutrition the patient was taken to surgery.

Employing simultaneous antegrade and retrograde dilatation of the longitudinal stricture, a 30F Maloney dilator was finally passed into the stomach. The crural sling was approximated and a Nissen plication done. Postoperatively the patient was dilated with the smaller Maloney dilators and was able to swallow liquids and soft food. Following discharge dilation was done frequently during the first 6 months and monthly dilatations were continued to one year. At the end of this time a barium swallow showed marked narrowing of the distal one-third of the esophagus but surprisingly the patient had no difficulty eating soft foods (Fig. 21). He could not, however, tolerate solids. Weight gain took place and he remained in fairly good health until he died two and one half years postoperative, apparently from a myocardial infarction.

Comment. This elderly man presented with a far-advanced esophageal stricture in which the lumen was all but completely occluded. Had this patient not been of advanced age and relatively free of associated constitutional disease a colonic or jejunal interposition procedure would have been performed. It is surprising however, that operative dilatation and correction of reflux were effective to a great degree in alleviating his total obstruction and allowing him to eat a restricted diet.

Results and Followup

Sixteen of the 17 patients survived operation and have been carefully followed. One patient, a 72-year-old man

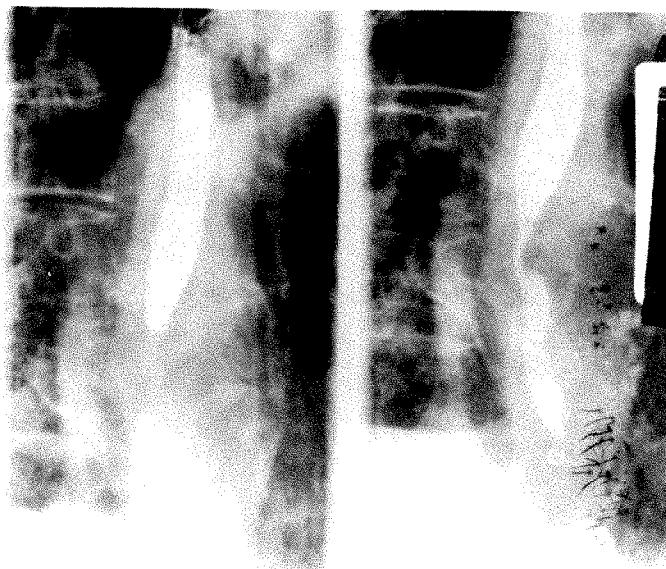
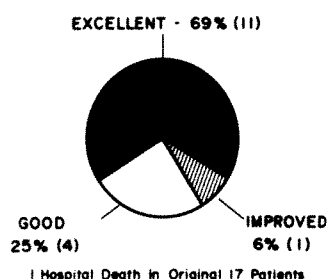


FIG. 21. Case 9: Postoperative barium study after one year shows diminution in the caliber of the previously dilated proximal esophagus. The strictured area still persists, but the esophageal lumen throughout this area shows considerable improvement as compared to the preoperative state. In spite of some persistent esophageal narrowing, this 90-year-old patient was able to take a restricted diet, gained weight, and was markedly improved.

FIG. 22. Follow-up results for 16 patients.



with pre-existing cardiac disease developed a cerebrovascular accident during the early postoperative period and expired. Two patients have since died of unrelated causes, each two and one-half years postoperative but are included in the followup. Each living patient has been observed at frequent intervals and esophagoscopy and barium contrast studies of the upper gastrointestinal tract have been part of the postoperative evaluation.

Eleven patients have obtained an excellent clinical result, experience no upper abdominal discomfort, and have no dietary restrictions. Four patients are termed a good result since each experiences mild and intermittent abdominal discomfort. One of the 4 has subjective evidence of reflux but esophagoscopy shows no demonstrable reflux or esophageal mucosal changes. This patient had a Belsey repair as the antireflux procedure in contrast to most of the group who underwent a Nissen fundoplication. Another patient with a good result had undergone a prior operation for reflux and also had a leiomyoma removed from the esophagus. The third patient listed as a good result had almost complete esophageal occlusion prior to operation. The fourth patient, likewise, presented with a far-advanced longitudinal stricture. Following dilatation and correction of reflux he has tolerated soft foods well but certain solid foods cause mild upper abdominal distress.

The 90-year-old man with total or near-total esophageal occlusion obtained a satisfactory or acceptable clinical result. Swallowing was restored, weight gain took place, but over the two and one half years that he survived his dietary intake was somewhat restricted and selective (Fig. 22).

During the postoperative followup 6 patients required from one to three esophageal dilatations during the early postoperative course, and two patients with severe longitudinal strictures required monthly dilatations up to one year.

One patient among the group has now been followed 3 years, two patients have been observed between 2½ and 3 years, two patients have been followed 2 to 2½ years, six patients have been followed 1 to 2 years, and five

patients have been observed during a rather short period of 6 to 12 months (Fig. 23).

Discussion

Resectional procedures and esophagogastroplasties have been widely used for correction of advanced reflux strictures. Although such operations have generally resulted in long term satisfactory results, operative morbidity and mortality have been distracting features. The decision to employ these procedures has usually been made on the basis of preoperative esophagraphy and endoscopic studies.

Hayward,¹³ in 1961, aware of the disadvantages of resectional operations, reported 14 consecutive cases of far-advanced reflux stricture treated by intraoperative dilatation with a concomitant antireflux procedure. He employed mainly the left transthoracic approach and advised forceful dilatation of the stricture from above with simultaneous dilatation *via* a gastrotomy using Hegar dilators. He emphasized that with a tight, fibrotic stricture and periesophagitis, the muscular coat of the esophagus in the strictured area was always less involved with the inflammatory reaction, and by splitting the stricture from within, an adequate lumen could be restored. *He decried the widespread delusion that abnormal fibrous tissue is of necessity permanent, and showed that following correction of reflux the damaged esophagus could be restored to normal or near-normal function.*

The magnitude of many operations for correction of reflux stricture with the associated morbidity and mortality prompted Hill to apply the simplified technique of intraoperative dilatation and posterior gastropexy. In 1970 he reported 36 cases with 85% good to excellent results. Twenty-five of his patients presented with longitudinal strictures, some extending proximally to the

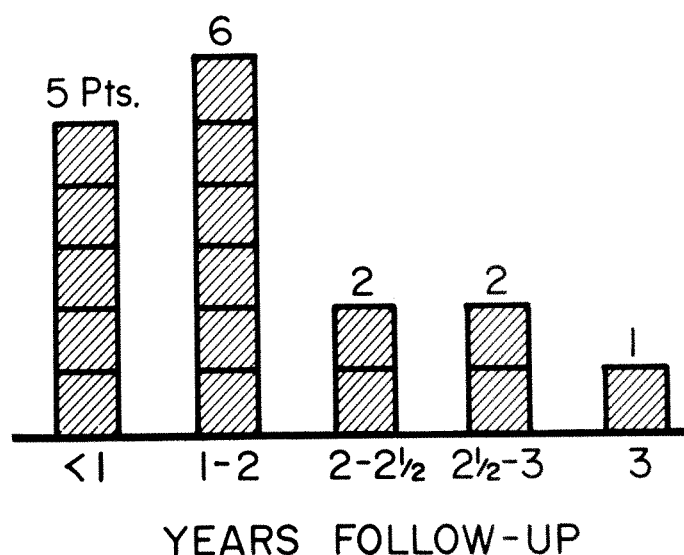


FIG. 23. Length of follow-up: 2 patients died 2½ yrs post op.

aortic arch. This outstanding contribution and Hill's continuing experience and excellent results serve to demonstrate that the current widespread use of more radical procedures may at times be unwarranted.

Moran²¹ obtained excellent results in 8 of 10 cases of advanced reflux stricture by intraoperative dilatation and a Belsey Mark IV antireflux procedure. From his experience he felt that the real nature of a stricture could be assessed only at surgery and many advanced strictures of long standing could be satisfactorily managed by this conservative approach. He showed that lower esophageal sphincter (LES) pressure was improved by the antireflux operation, but felt the most important factor in preventing reflux was the creation of an effective valve at the gastroesophageal junction.

Recently Safaie-Shirazi^{31,32} reported 26 cases treated by dilatation and fundoplication with excellent results over a followup from 6 months to 7 years. It is of interest that recently Neaf²² described 27 patients with esophageal stricture, many far-advanced, who were treated with a Nissen fundoplication without associated instrumental dilatation. Each patient experienced relief of symptoms and the stricture underwent resolution. Neaf felt that major resectional operation for stricture was unwarranted except in the very rare case. Larrain²⁰ of Chile has likewise treated advanced strictures with an antireflux operation without stricture dilatation.

One may rightly argue that not all far-advanced reflux strictures can be satisfactorily managed by a conservative surgical approach. However, many patients with severe strictures have unquestionably been subjected to radical procedures when a simplified method would have sufficed.

Our current experience with 17 *consecutive* cases demonstrates the fallacy of selecting a particular operative procedure on the basis of preoperative studies alone. Preoperative dilatation was attempted in a few of the short annular strictures in our group, but was not performed with the advanced longitudinal stricture. At operation, patience and perseverance were found to be important keywords to successful dilatation. At the onset in some cases it was felt that dilatation would be impossible, but by using repeated, forceful maneuvers controlled from above and below, success was ultimately achieved. Several of the longitudinal strictures were several centimeters in length but others were shorter, and preoperative barium studies were of little value in assessing stricture length.

Several of the longitudinal strictures did not extend distally to the level of the esophagogastric junction.

In two patients following dilatation and correction of reflux, the esophagogastric junction could not be brought below the diaphragm without tension. Therefore, a portion of the Nissen fundoplication was left in the posterior

mediastinum. Some authorities stress the importance of securing the gastroesophageal junction in an abdominal position to ensure against reflux,^{15,36,37,41} but others have shown experimentally and clinically that intrathoracic fundoplication results in an elevated LES, an alkaline esophageal pH, and normal acid clearing.^{5,7,10,21,35}

Butterfield,⁵ in extensive autopsy studies, demonstrated that fundoplication prevents reflux on a mechanical basis, much like a one-way flutter valve, and this effect is the same whether the repair is cephalad or caudad to the diaphragm. Safaie-Shirazi³³ and Woodward⁴² have each shown at operation that if adequate fundoplication is done, saline introduced into the stomach *via* a nasogastric tube cannot be made to regurgitate above the repair when forceful manual pressure is applied to the gastric wall against an occluded pylorus. Cohen and Harris⁷ demonstrated clinically and experimentally that the LES response to an increase in gastric pressure would seem to be unaffected by the location of the gastroesophageal junction above or below the diaphragm and to be unaffected by surrounding pressure. Safaie-Shirazi³⁴ has demonstrated the effectiveness of intrathoracic fundoplication and even when performing intra-abdominal fundoplication, demonstrated no benefit by adding crural sling repair. Each of the 17 patients in the current study had an associating sliding hiatus hernia. An increasing number of reports are appearing which convincingly show that there is no relationship between esophageal hiatus hernia *per se* and reflux. A substantial number of patients with hiatus hernia fail to demonstrate evidence of reflux and up to 20% of patients with reflux have no demonstrable hiatus hernia.

Ninety four per cent of the patients under consideration have obtained a satisfactory result with the majority being free of alimentary tract symptoms. The complaints among five patients are indeed small in comparison to the preoperative symptomatology. Postoperative dilatations have been few and infrequent except in two cases and they have posed no problem to the patient.

During the long-range postoperative followup esophagography and endoscopy have demonstrated an increase in the caliber of the esophageal lumen as compared to immediate postoperative studies. Restoration of the esophageal mucosa has also been observed. Eleven patients have now been followed from one to 3 years and 5 patients from 6 months to one year with no evidence of recurrent stricture formation.

It would appear that this simplified surgical approach directed toward correction of reflux and preservation of organ tissue should be attempted before resorting to more radical forms of surgical therapy. Our current experience, along with that of others, serves to demonstrate that many advanced fibrotic strictures may be managed by this method.

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DISCUSSION

DR. R. B. WELBOURN (London, England): The members of the gastrointestinal unit in my own Department, at the Royal Postgraduate Medical School at Hammersmith Hospital, have great interest and considerable experience in esophageal reflux with stricture, and it is their work to which I will refer. We agree that resection or other heroic operations are very rarely needed for this condition. However, we consider that the length of the stricture is immaterial in relation to management. In our experience most strictures due to reflux are short and long ones should be suspected of malignancy.

Dick Franklin and his colleagues reported in 1973 on the results of treating 26 patients with hiatal hernia and stricture. Most of them were aged 40–80 years and several had had previous operations. They used dilatation via a rigid esophagoscope together with Nissen fundoplication. We have found this operation the best procedure to use at the cardiac end of the stomach for the prevention of reflux. I will refer to another at the pyloric end shortly. Of the 26 patients, 1 died, 4 failed to

obtain relief, 5 were improved and 17 were relieved completely. Therefore in 22 (81%) the results were worthwhile. The followup was from 6 months to 3 years, but our experience is that recurrences usually occur early in this disease so that the long-term results are unlikely to be very different.

Recently Chris Royston and John Spencer have been using Eder-Puestow dilators passed through a flexible endoscope. A flexible wire guide is passed down the endoscope through the stricture, and the endoscope is then withdrawn. Progressively larger dilators are then threaded over the wire until the desired degree of dilatation has been obtained. The procedure may be done on outpatients under intravenous sedation and, as a refinement, under X-ray control. It can be repeated easily and is suitable as the only treatment for elderly and infirm patients. Royston and his colleagues in Northampton and Gloucester have just analyzed their experience of 51 dilatations in 26 patients. They find the procedure much easier and safer than dilatation through the rigid endoscope. All the patients were relieved immediately, one developed inhalation pneumonia, but there were no perforations or deaths. This is

the form of dilatation which we now use with Nissen fundoplication.

There remain a few patients who fail to respond to these procedures. We have been impressed by the evidence of Wally Gillison that esophagitis is due to reflux of duodenal contents rather than of gastric juice, and we have been encouraged by the results of Large and his colleagues who, after resecting the stricture and doing a vagotomy performed distal gastrectomy with a Roux-en Y anastomosis to ensure that the duodenal contents were diverted from the stomach and esophagus. But we have simplified this procedure, using Eder-Puestow dilatation instead of resection, and then doing the antrectomy with the Roux-en-Y procedure. Occasionally it is not possible to pass the dilators from above, but then they can be passed from below at operation. Royston and Spencer have done this operation in 8 patients. Six had had previous operations and 1, who had not been able to swallow anything, had required gastrostomy feeding for 6 months. Of these 8 patients, 1 (a very frail octogenarian who developed bronchopneumonia) died and 7 were cured. Of these, 4 required no further dilatation, 2 required 1, and 1 required 2 dilatations.

Before we started using the Eder-Puestow dilators, we regarded failure of a stricture to take a dilator of French gauge 16 as an indication for resection. Now we are coming round to the view that resection is never needed. This may be too optimistic, but it is our hope.

DR. LUKE HILL (Seattle, Washington): I think we have heard a milestone for those of us who have been interested in reflux strictures of the esophagus.

Some of you may recall that in 1970 we presented our concept of a simplified management of this very difficult problem. We presented 37 patients, 25 of whom had tight strictures. After a simplified procedure we found that these strictures would heal with surprising rapidity if reflux was corrected. This is the GI series on that same patient one year later. We have followed these patients now, some of them, for as long as eight to nine years, and they have remained well.

Since the paper was presented, a great deal of controversy, and even criticism, has been aimed at us because this report tread on such allowed surgical principles as the short esophagus and the so-called undilatable stricture. Now that Dr. Herrington and his group, a group of renowned reputation, have come forth with a very clear presentation, hopefully the controversy will come to an end.

In the text of Dr. Herrington's paper he indicates that about five of his patients had some reflux and some persistent narrowing, even though all 17 patients were relieved of their stricture. We, too, had some persistent reflux early in our experience, and in an effort to offset this, we have over the last year and a half been measuring the barrier, or sphincter, pressure at the time of operation by simply passing a polyethylene tube with a side hole connected to a pressure-sensing device up and down across the g.e. junction. We persist in narrowing the cardia until we have reached a sphincter pressure as you see it here, of around 41 mm of mercury.

The proof of the pudding is that in all of these patients so treated—and we have measured now 44 of them postoperatively over the last year and a half—none of them reflux; and the patients are relieved of their symptoms.

We also note that this procedure increases the length of the sphincter.

We disagree with Lynwood in only one respect. We use the posterior gastropexy more often than he does, because we feel it gives us a better opportunity to accurately calibrate the cardia and reach the desired sphincter pressure, and, hopefully, to overcome the problem of persistent reflux after what appears to be a technically good operation.

These comments simply underscore what Dr. Herrington and his group have said, however, and if his paper accomplishes what I hope it will accomplish, surgeons throughout the country will no longer feel compelled to resect or do a formidable procedure when a simplified approach, as he has so clearly indicated, will relieve these unfortunate patients of their stricture.

DR. J. HARVEY JOHNSTON, JR. (Jackson, Mississippi): This excellent paper is timely, beautifully presented, factual, and probably provocative. Our experience supports the authors' concept of conservative surgical management of reflux esophageal strictures; that is, dilatation of the stricture with antireflux procedure (preferably a Nissen) as initial therapy, reserving esophagofundoplasty and intestinal interposition for the infrequent failure of the more conservative approach, or for the exceptional massive transmural stricture. Resection of the usual stenosis has proven unnecessary, for dilatation yields satisfactory results in over 90 percent of cases.

Digital fractures of the stricture by means of the index finger inserted through a small gastrotomy opening just distal to the esophagogastric junction has proved eminently satisfactory in our hands. This allows for far more accurate assessment of esophageal stenoses than does instrumentation. We have had to revise our concept of the frequency of longitudinal strictures, for we now find that four out of five esophageal strictures are of the short, annular, or diaphragmatic type, usually not exceeding 1 cm in length.

Many strictures classified as longitudinal by conventional means of evaluation are in reality short, annular, diaphragmatic strictures, responding readily to dilatation. Following finger fracture, a balloon catheter of the Foley type is inserted through the gastrotomy opening for pneumatic dilatation of the esophagus under direct vision. Fundoplication reinforces the gastrotomy opening, making leakage a rarity.

Operative appraisal of esophageal strictures is of paramount importance; yet it should be emphasized that evaluation of degree or length of a stricture by external inspection and palpation of the esophagus can be quite misleading.

Although admittedly selective, and treating older, poor risk patients by dilatation alone—no surgery—our group has treated a series of approximately forty esophageal stenoses with conservative surgery, with no mortality. One was closed and buttressed with fundoplication, and the patient had a perfectly smooth convalescence. The other was a dense and fibrotic stricture, and was successfully treated by resection and esophagojejunostomy of the Roux-Y type, deliberately bypassing the stomach because of marked obesity.

Postoperative dilatation is usually not necessary. Thus far there have been two failures from conservative surgery. One represents a failure of the Allison anatomic repair, dramatically improved by adding Nissen fundoplication. The other enjoys a good result following an esophagofundoplasty of the Thal-Woodward type, and that patient stated we waited too long to do it.

DR. JOHN L. SAWYERS (Closing discussion): We appreciate the remarks of our honored guest, Professor Welbourn, regarding his experience in London, and are pleased that he agrees with the concept that the anti-reflux procedure is the key to success in this operation. We're also pleased to hear about his work with the Elder-Puestow dilators for those patients who cannot withstand operation. This is a useful method for palliating their obstructive symptoms.

We're very indebted to Dr. Hill, who has been a pioneer in this country in introducing the conservative surgical management for this condition. He really diverted us from the resection and interposition procedures to use his particular method, and we're pleased that it has been so successful.

For those of you who do not have his sophisticated measurements, a simple intraoperative test that Dr. Ed Woodward described several years ago to determine whether the reflux procedure is competent is to instill 150 cc of saline into the stomach, temporarily occlude the pylorus, bring the nasogastric tube back up into the esophagus and manually compress the stomach with the instilled saline; and if the saline doesn't reflux back up through the nasogastric tube, then the procedure is satisfactory.

Cardiac Contusion: A Capricious Syndrome

JAMES W. JONES, M.D., ROBERT L. HEWITT, M.D., THEODORE DRAPANAS, M.D.

Cardiac contusions are being recognized with increasing frequency. Among 507 patients with non-penetrating chest injuries, 210 had serial electrocardiograms sufficient to evaluate the heart. Forty-five of these 210 patients (21%) had cardiac contusions. These 45 patients and 3 others who were confirmed to have cardiac contusions at necropsy, comprise the 48 patients in this series. Life-endangering cardiac complications occurred in 14 (29%) of the 48 patients, and 4 patients died. The development of cardiac complications following cardiac contusions appears to have a significant relationship to the presence of shock, hypoxia and to factors related to the severity of multiple injuries. These observations have therapeutic implications in management of patients with cardiac contusions through prevention of hypovolemia and hypoxia and avoidance of fluid overload as well as treatment of specific cardiac complications.

A SPECTRUM of cardiac injuries may result from non-penetrating chest trauma including rupture, chamber fracture, fracture of the valvular structures and contusion of the myocardium. Although cardiac contusion is usually non-fatal, it may be accompanied by a variety of potentially fatal complications.^{4,7,8} Furthermore, cardiac contusion may be unrecognized initially and may become apparent only when a serious cardiac complication develops. This retrospective study was undertaken to evaluate the frequency and type of complications in patients with documented cardiac contusion and to determine if a high-risk subgroup likely to have serious cardiac complications could be identified.

Patient Selection

The records of 507 patients with non-penetrating chest injuries admitted to the Tulane Surgical Service, Charity Hospital of Louisiana from 1963 through 1973 were reviewed. Forty-eight patients (9.4%) of the 507 patients were identified as having cardiac contusions. Among those 507 patients with non-penetrating chest injuries, 210 patients had serial electrocardiograms sufficient in

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number and timing to properly evaluate the heart. Forty-five (21%) of these 210 patients had cardiac contusions. Criteria for diagnosis included definite electrocardiographic evidence of injury which completely or partially resolved on subsequent electrocardiograms following injury. These 45 patients and three others, confirmed to have cardiac contusion at necropsy, comprised the 48 patients in this study. Patients with valvular injuries, myocardial rupture and traumatic septal defects although also related to trauma were not included.

Results

The frequency of the diagnosis of cardiac contusion during the period of study is indicated in Figure 1. An increasing awareness of this injury is apparent by the increase in number of patients with myocardial contusions admitted to the hospital during this time although the diagnosis was established in 17 patients 48 hours or more following admission to the hospital.

The patients in this series were predominantly young males who were involved in automobile accidents. Thirty-nine were males, and the average age was 33 years. Table 1 lists the modes of injury for the 48 patients, and as indicated, vehicle accidents accounted for injury in 45 patients.

Table 2 lists the associated injuries in the 48 patients. Most sustained multiple injuries, averaging 2.7 injuries per patient. Evidence of moderate to severe chest trauma was apparent in all patients as determined by history, physical examination or roentgenogram. As listed, 22 patients had rib fractures and 13 had sternal fractures. Pulmonary contusion, hemothorax and pneumothorax were also common. Associated non-thoracic injuries were also common, especially injuries to the abdomen, pelvis and cranium. Auscultation of a pericardial friction

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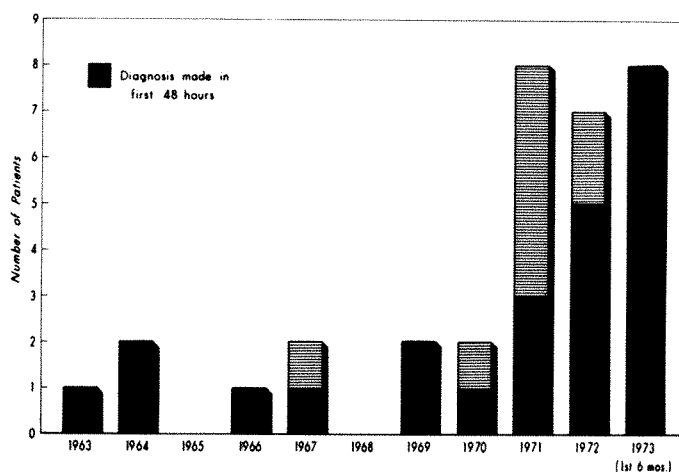


FIG. 1. Forty-eight patients with cardiac contusions admitted to Charity Hospital, 1963 through 1973; the diagnosis was established 48 hours or longer following admission in 17 patients.

rub or abnormality in heart sounds were documented in only 11 patients. Heart size usually remained normal on roentgenogram unless the injury was accompanied by pericardial effusion.

Serial electrocardiograms were the most reliable method of establishing the diagnosis of cardiac contusion. Electrocardiographic changes were predominately in the ST-segment and T-wave in 40 patients. QRS abnormalities or Q waves were observed in 9, and conduction abnormalities were observed in 7. Typical electrocardiographic changes are demonstrated in Figures 2, 3 and 4. The electrocardiographic abnormalities were temporary in most patients and usually resolved to a normal pattern within two to three weeks.

Life-endangering cardiac complications occurred in 14 of the 48 patients with cardiac contusion. A number of other patients developed lesser cardiac complications which did not require treatment such as sinus tachycardia, premature ventricular contractions or conduction disturbances which were not severe such as right bundle branch block in 5 patients and left anterior hemiblock in two.

The complications considered to be life-endangering all required treatment and are listed in Table 3. The early complications included arrhythmias which required pharmacologic treatment (atrial fibrillation, atrial flutter, supraventricular tachycardia and ventricular tachy-

TABLE 2. Specific Injuries Among 48 Patients With Cardiac Contusions

Chest	
Rib Fractures	22
Sternal Fracture	13
Flail Chest	7
Clavicle Fracture	4
Mediastinum; great vessel injury	7
Pulmonary contusion	18
Hemopneumothorax	11
Abdomen	
Liver Fracture	6
Spleen Fracture	3
Retroperitoneal Hematoma	1
Diaphragmatic hernia	1
Hepatic veins	1
Cranial Injury	14
G-U Injury	13
Pelvic Fracture	3
Long Bone Fracture	7
Spinal Fracture	3
Facial Injuries	3
Total	133

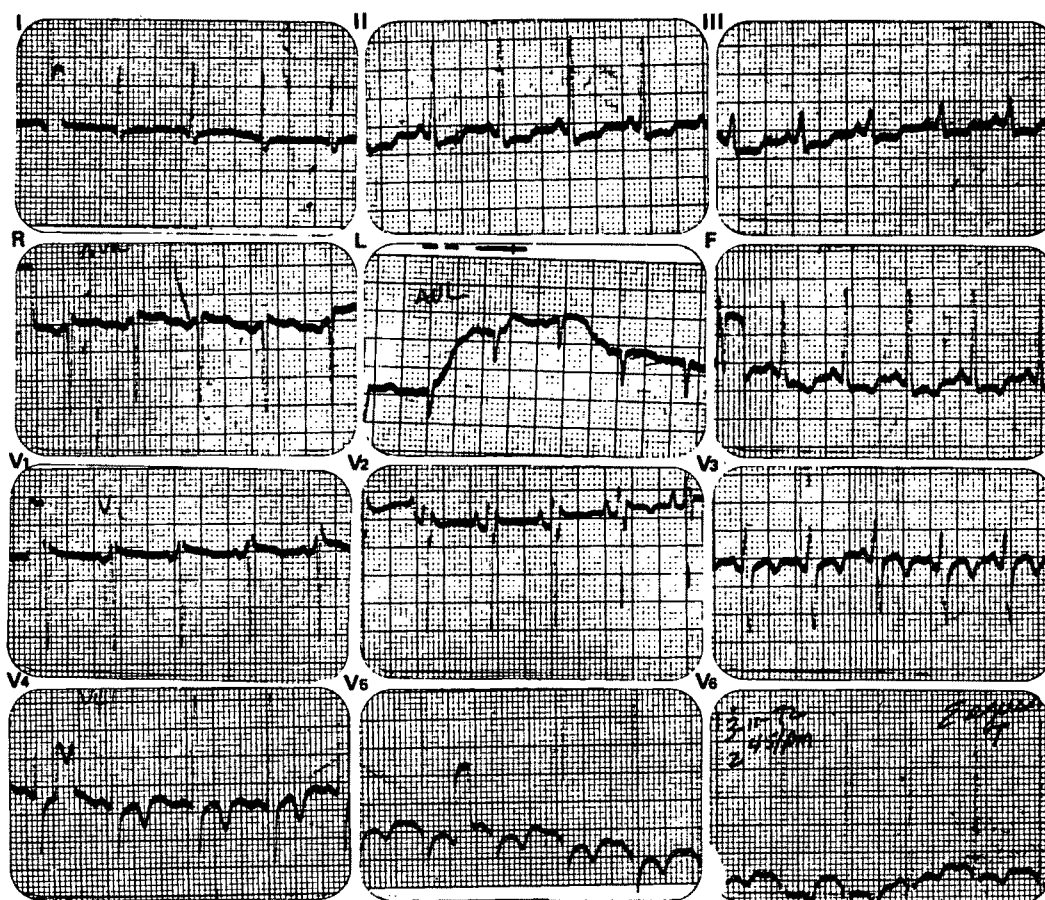
cardia), heart failure and complete heart block. Four patients subsequently developed pericardial tamponade requiring pericardiocentesis, and 3 of them required pericardial window or pericardectomy. One patient required pericardectomy for constrictive pericarditis.

The group of patients with severe cardiac complications appeared to include the more severely injured patients since these 14 patients had an average of 3.36 extracardiac injuries per patient as compared to 1.91 injuries per patient for the group without cardiac complications ($P < 0.05$). This observation suggested two possibilities: either the cardiac damage *per se* was more serious or perhaps the presence of shock, hypoxia or other factors related to the severity of the multiple injuries contributed to the subsequent development of cardiac complications in patients with cardiac contusions (Table 4). To answer this question, computer analysis was undertaken to determine a possible relationship between the subsequent development of cardiac complications and the presence of shock defined as systolic blood pressure less than 90 mm Hg and between subsequent development of cardiac complications and the presence of hypoxia as defined by blood gas analysis and need for respiratory support. Significant complications of cardiac contusions were related to both shock and hypoxia. Cross analyses among 23 different injury variables also indicated that cardiac complications were related to certain specific injuries, including flail chest, liver injury, splenic injury and pelvic fractures. No other specific injuries were statistically related to shock, hypoxia or development of cardiac complications, and no correlation was found between the presence of cardiac complications and age of the patient.

TABLE 1. Cardiac Contusion: Mode of Injury

Mode	Patients
Automobile Accident	38
Pedestrian Accident	4
Motorcycle Accident	3
Fall	3
Total	48

FIG. 2. Electrocardiogram 4 hours following injury demonstrating evidence compatible with cardiac contusion. Abnormalities include; sinus tachycardia; low T_1 , diphasic $T_{2,3}$ with ST segment depression and inverted $T_{4,5,6}$ with ST segment depression. Prominent $R_{V_{5,6}}$ and $S_{V_{1,2}}$ are also noted.



Four patients among the 48 in this series died, 3 as the result of cardiogenic shock and one as the result of brain injury. All 3 patients who died from cardiogenic shock were confirmed to have cardiac contusions and evidence of cardiac failure and pulmonary edema at necropsy. The

average hospital stay for the 44 surviving patients was 21 days.

Comment

Previous studies have documented the occurrence of heart injury following non-penetrating chest trauma and have established the present concept that cardiac contusions are common and rarely fatal.^{2,4} Cardiac injury has also been estimated to represent the most common unsuspected visceral injury responsible for death in fatally injured accident victims.⁷ Furthermore, cardiac contusions are among the most frequently missed or delayed diagnoses in injured patients admitted to the hospital. The reasons for delay in diagnosis are often related to 1) attention directed toward other severe injuries, 2) lack of evidence of thoracic injury and, 3) lack of evidence of cardiac injury on initial examination. Frequently electrocardiographic signs of cardiac contusion may not be apparent until 24 hours or more after injury.¹² Data from the present study indicate that although cardiac contusion is now being recognized with increasing frequency the diagnosis is still often delayed 48 hours or more following injury in a significant number of patients.

The clinical and diagnostic features of cardiac contusion are similar to those of myocardial infarction. Chest pain is common and often indistinguishable from angina

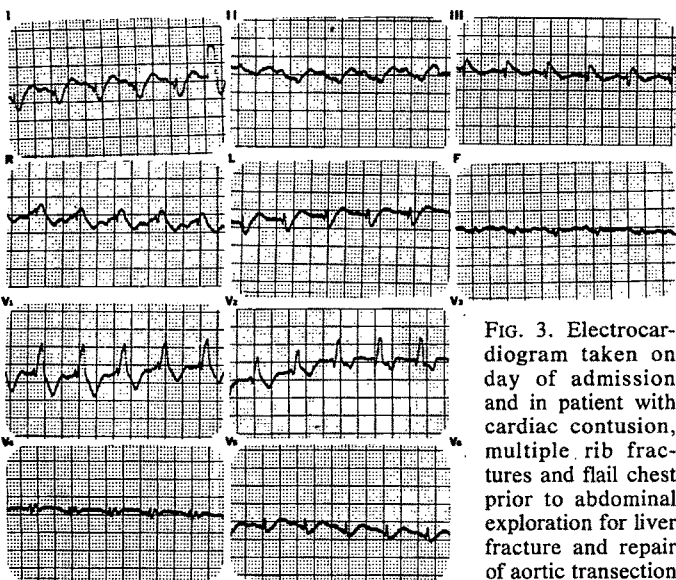


FIG. 3. Electrocardiogram taken on day of admission and in patient with cardiac contusion, multiple rib fractures and flail chest prior to abdominal exploration for liver fracture and repair of aortic transection and traumatic aneurysm of descending thoracic aorta. Abnormalities include sinus tachycardia, right bundle branch block and $Q_{1,2,V4,5}$.

rysm of descending thoracic aorta. Abnormalities include sinus tachycardia, right bundle branch block and $Q_{1,2,V4,5}$.

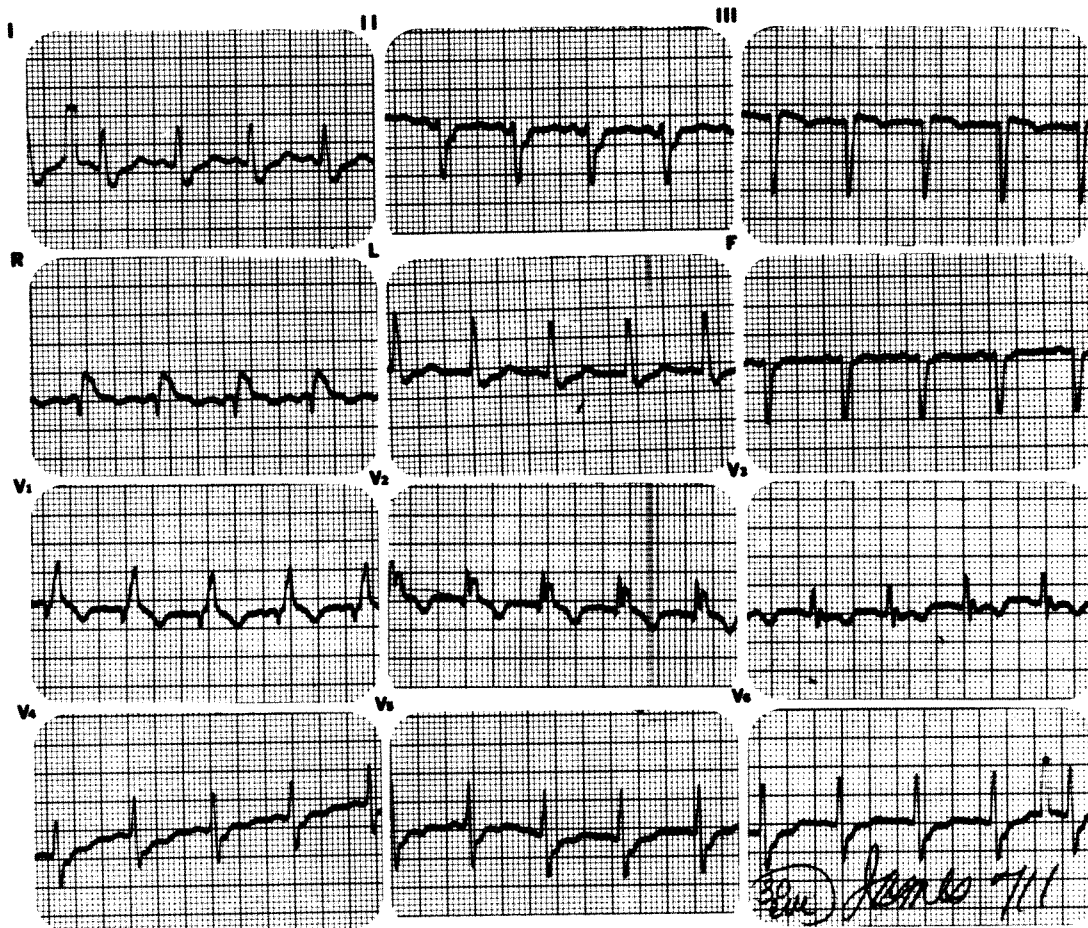


FIG. 4A. Electrocardiogram in patient with cardiac contusion on day of admission demonstrating: depressed ST segment in $V_{5,6}$, Q_3 , low $T_{2,3,4}$ and right bundle branch block.

Since most patients have concomitant chest wall injury and pain, the pain related to cardiac contusion may be difficult to interpret. The diagnosis is usually not made on physical examination in the absence of tamponade, arrhythmias or heart failure. Electrocardiography is the most accurate method of establishing the diagnosis of cardiac contusion in severely injured patients as it was in 45 of the 48 patients in this study. The incidence of electrocardiographic evidence of cardiac injury following blunt chest trauma has been estimated to be from 17% to 38%.¹² In the present study, 45 (21%) of 210 patients with serial electrocardiograms demonstrated cardiac contusions. These observations emphasize the need for obtain-

ing serial electrocardiograms in all patients evaluated for severe non-penetrating thoracic trauma. An increase in

TABLE 3. Life-endangering Cardiac Complications Among 14 Patients With Cardiac Contusion

	No. Complications
Early	
Arrhythmias	6
Congestive Heart Failure	5
Complete Heart Block	2
Intermediate	
Tamponade	4
Late	
Constrictive Pericarditis	1
Total	18

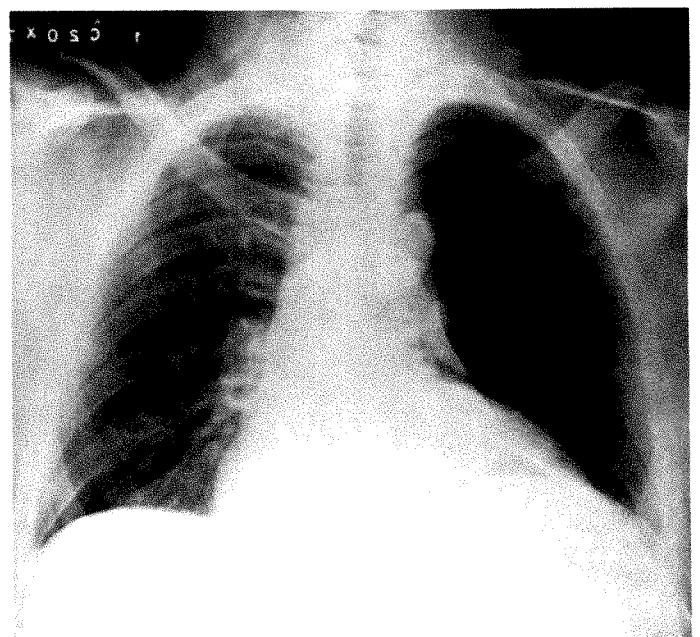


FIG. 4B. EPA chest roentgenogram same patient as in Fig. 4A.



FIG. 4C. Lateral chest roentgenogram demonstrates fracture of sternum.

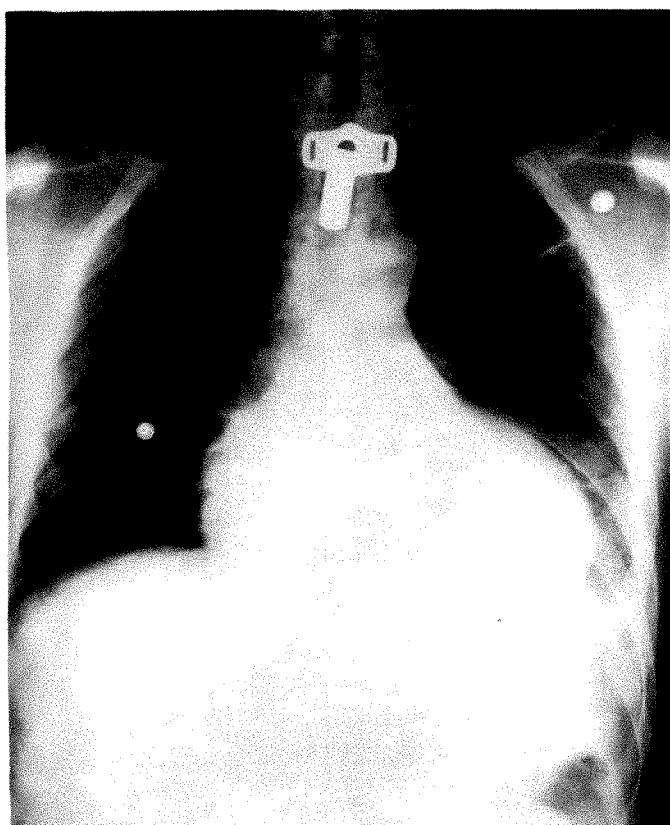


FIG. 4D. EPA chest roentgenogram taken 3 weeks following injury demonstrating cardiac enlargement due to pericardial effusion, which required pericardiocentesis and ultimately pericardial window.

TABLE 4. Occurrence of Hypotension and Hypoxia in Patients With and Without Serious Cardiac Complications of Cardiac Contusions

	Total Patients	No. Patients Hypotension	No. Patients Hypoxia
Cardiac Complications	14	11	8
No Cardiac Complications	34	6	5
Total	48	17	13

the number of patients adequately evaluated by electrocardiography is the major factor in the increased frequency of diagnosis observed in this report. Our experience confirms that of others in that the most frequent electrocardiographic changes in cardiac contusion are ST segment and T wave changes which are similar to those changes observed in myocardial ischemia and infarction.^{3,11,12} These electrocardiographic changes are usually reversible but may persist for several weeks following injury. Permanent changes may be associated with more severe injuries.

In contrast to reports of the frequent absence of external chest wall damage⁸ all 48 patients in this series had evidence of moderate to severe trauma to the thorax apparent from either physical examination or roentgenograms. Twenty-two patients had associated rib fractures and 13 had sternal fractures. Aside from evidence of significant chest wall injury, the only other physical signs helpful in establishing the diagnosis were presence of a friction rub or abnormality in heart sounds.

Serum enzyme levels (SGOT, LDH and CPK) were evaluated in approximately one-third of patients in this series and although elevated in most patients were of no value in establishing the diagnosis of cardiac contusion. Others have emphasized that serum enzyme elevations due to concomitant injuries of liver, lung, bone brain and skeletal muscle may obscure elevations due to cardiac injury.⁷ Furthermore, elevations in SGOT and LDH may be associated with blood loss and metabolic acidosis which would limit use of these enzyme levels in evaluating cardiac injury in severely injured patients. Presently, we are evaluating the usefulness of CPK isoenzyme levels in such patients. Pomeranz and Eiseman demonstrated that low cardiac output as measured by impedance cardiography may be the most sensitive index of cardiac contusion.⁹ However, this technic may be difficult to apply in some patients with thoracic injury. Serial cardiac output determinations using dye dilution technics or thermal dilution technics are often not available in these severely injured patients although their use may be sometimes practical and desirable. Technetium scan has also been suggested as a possible diagnostic technic for cardiac contusion.^{5,11} Although we are presently evaluating that technic in patients with suspected

cardiac contusions, our experience is presently too limited to advocate its use.

Our data also indicate that serious cardiac complications of cardiac contusion are more likely to be seen in patients with shock and hypoxia. These observations suggest that the contused myocardium has a loss of reserve which may not be detectable except during periods of stress and increased oxygen demand such as hypovolemia and hypoxia. The contused myocardium may be unable to respond with an appropriate cardiac output under these conditions and may be more vulnerable to development of arrhythmias during such periods of stress. The cardiovascular effects of the autonomic nervous system and particularly the effects of elevated catecholamine levels upon the contused myocardium during these stresses should also be considered.

Eiseman and his associates have suggested that myocardial contusion may alter the cardiac response of a healthy young patient to resemble the heart of an aged patient with marginal cardiac reserve.⁶ Furthermore, hypotension due primarily to hypovolemia may be further compounded by pump failure due to the contused myocardium since an inappropriately low cardiac output is frequently found in patients with cardiac contusion.⁹ Pump failure therefore, may amplify shock due to hypovolemia and also further contribute to hypoxia. The therapeutic implications are, of course, obvious and include: 1) the appropriate correction of hypovolemia and hypoxia; 2) the avoidance of subsequent fluid overload; and 3) treatment of specific cardiac complications as promptly as possible.

Therefore, primary objectives in management of patients with cardiac contusion include prompt correction of hypovolemia and hypoxia and control of injuries which contribute to hypovolemia. As in any group of severely injured patients blood volume replacement, ventilatory support when indicated and operation to control blood loss from visceral injuries are essential, and the promptness of these interventions may be of critical importance in patients with cardiac contusion because of their diminished cardiac reserve. The potential for the contused heart to develop arrhythmias, low cardiac output and pump failure emphasizes the need for careful cardiac monitoring in such patients. Electrocardiographic monitoring should be continued throughout any critical period of the patient's course. Monitoring of central venous pressure or pulmonary artery pressure is useful, but this information must be carefully interpreted since many of the patients will have pressure alterations as a consequence of pulmonary abnormalities associated with shock, thoracic injury or non-thoracic trauma. In some patients the use of a Swan-Ganz catheter wedged in a small pulmonary artery may be helpful to reflect alterations in left atrial pressure and, therefore, left ventricular

function when primary pulmonary changes do not obviate its accurate reflection of left atrial pressure. The present experience does not include use of the Swan-Ganz catheter in patients with cardiac contusion although we are presently evaluating its use in such patients.

Prompt recognition and treatment of specific cardiac complications are also important. Supraventricular arrhythmias which required treatment were most often managed by digitalis while ventricular arrhythmias were usually managed with lidocaine. Congestive heart failure was managed with digitalis, diuretics and fluid restriction. Four of the 5 patients with pump failure observed in this series developed congestive heart failure within 24 hours of admission to the hospital during periods of intravenous fluid replacement, and two of these patients died.

The avoidance of fluid overload in management of patients with cardiac contusion cannot be overemphasized and is an important indication for careful monitoring as discussed. Others have advocated use of anticoagulants in patients with cardiac contusion and persistently low cardiac output.⁹ We avoid use of anticoagulants in all patients with cardiac contusion since most patients do have other significant injuries which may be complicated by anticoagulants. Furthermore, the effects of anticoagulation upon the cardiac injury are uncertain and may be risky in patients with cardiac contusions accompanied by hemopericardium. An exception is the temporary use of heparin for partial cardiopulmonary bypass as used in one patient in this series for repair of a transected thoracic aorta. The use of anesthetics and drugs which may result in myocardial depression or irritability should be avoided whenever possible. Careful attention should also be directed toward prevention and correction of electrolyte abnormalities.

Patients with the diagnosis of cardiac contusion should be followed carefully since delayed complications may appear months or years later. Doty and associates recently reported upon a group of 8 patients studied by cardiac catheterization and left ventricular angiography 2 weeks to 5 years following myocardial injury.⁵ A ventricular septal defect was detected and repaired 3 weeks after injury in one patient and left ventricular aneurysms were resected from 34 to 68 months after injury in 3 others. No patients in the present series were found to have ventricular septal defects, and none have as yet been documented to have ventricular aneurysms although many of these patients are not available for long term followup. Stern and associates have recently reported upon a 16-year-old patient with occlusion of the left anterior descending coronary artery as a result of blunt trauma documented by cardiac catheterization and cineangiography approximately 3 months following injury.¹² No patients in the present series were suspected

or documented to have coronary artery occlusion as a result of trauma.

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DISCUSSION

DR. JAMES D. HARDY (Jackson, Mississippi): This is an excellent paper, and the many patients surveyed have been beautifully analyzed. I would like, Dr. Hewitt, to devote my remarks to an even more subtle situation than you have emphasized, although you have touched upon it in your paper. I refer to the patient who has sustained a deceleration accident but who initially appears to have escaped serious injury. Two cases will be cited.

The first patient was treated by a colleague of mine for what appeared to be a relatively minor motor vehicle accident. He was kept overnight or perhaps 48 hours and then sent home. About 10 days later, apparently while discussing a suit against the person who hit him, he fell dead across the lawyer's desk. Autopsy disclosed that he had originally ruptured the aorta just above the heart; final rupture of the adventitia had precipitated sudden death from pericardial tamponade.

(Slide) The second patient was a 15-year-old girl, not originally my patient. In fact, the anesthesiologist covering the ICU that night called me and said he wished I'd come down and see a young girl who just looked "sour," somehow or other, without clear evidence as to what was wrong. She had been driving a Volkswagen, and her chest had hit the steering wheel when she collided with another car. There was almost no ecchymosis over her sternum, no rib fractures, no sternal fractures. The chest x-ray looked all right. The abdomen was considered to be negative. Yet she just didn't look right.

I saw nothing obvious either, but I suggested that we insert a nasotracheal tube, so that we would have control of the respiration if something happened. Presently, though, she began to exhibit pulsus paradoxus. We aspirated the pericardium twice, got nothing, but just the same she clearly had developed a low cardiac output syndrome. Therefore, we took her to the operating room, made a small vertical incision over the xypoid area about the size one makes to put in a screw-in pacemaker, and saw that she had blood in the pericardium. The incision was then enlarged a bit, and it could be seen that, without any thoracic cage injury, this young girl had had her heart compressed so abruptly that the right atrial appendage had ruptured. All that was required was to place a clamp proximal to the point of rupture to control the bleeding, and then to repair the defect.

Thus, these patients can have serious cardiac injuries without having first rib fractures, sternal fractures, other fractures or multiple injuries. The point is acknowledged in your paper, but it has deserved further emphasis.

DR. KENNETH L. MATTOX (Houston, Texas): We were happy to review Dr. Hewitt's manuscript, which calls our attention to a very important diagnosis which is frequently overlooked. The incidence of cardiac contusion, as well as penetrating cardiac injury, is usually studied retrospectively. The true incidence of cardiac contusion in patients with remote injury, such as fractured femur, hip, et cetera, may be higher than the 21% alluded to here.

Many of our cities are now adding EKG telemetry to the emergency

medical service system; since July of 1974 we have identified several patients in Houston with remote blunt trauma to the extremities in whom ST segment changes and frank Q waves were seen before they arrived at the hospital, and in these patients resuscitative fluids are administered judiciously.

Prehospital cardiac telemetry may be usefully applied to the trauma patient, and its availability is now wide-spread. As mentioned in the manuscript, Stern and associates have recently documented a case of coronary artery injury and occlusion secondary to blunt trauma, which was treated conservatively. We recently had a patient with an isolated transection of the left anterior descending coronary artery secondary to a stab wound, but which brings up a potential treatment consideration including the patient in blunt trauma.

This patient sustained cardiac arrest upon arrival at the emergency center. He was placed on a battery operated cardiopulmonary bypass, and transferred to the operating suite, where he underwent proximal and distal ligation of the left anterior descending coronary artery at the injury, and saphenous vein bypass. There was immediate restoration of good contraction of a previously akinetic left ventricle some three hours post-injury.

Thus, selected patients with cardiac contusion may require cardiopulmonary bypass, or even cardiac assist, if pump failure occurs.

A medicolegal question is in order. A patient in the atherosclerotic, or older age group who was involved in an automobile wreck, and in whom ST changes are seen, or frank Q waves are seen at the hospital, is a sticky tort if litigation ensues. Which came first? Did the heart attack cause the wreck, or vice versa?

One must likewise ask: In a patient in this risk group is the stress of trauma and the shock itself sufficient to produce EKG changes, rather than myocardial contusion?

DR. BEN EISEMAN (Denver, Colorado): Cardiac contusion will be recognized following chest and upper abdominal injury in direct proportion to the compulsiveness with which it is sought. Fractures of the stern, first and second ribs almost always are associated with significant direct myocardial injury. There may be, however, a wide discrepancy between the severity of injury to the heart and the roentgenologic findings. As in Dr. Hardy's case, the chest wall of young people is so compliant that the sternum can crush the heart against the vertebrae and spring back again without leaving x-ray evidence of fracture. Not so, customarily, in the elderly.

The problem is to select the unimportant from the serious arrhythmias that follow, in the 1-3 days following severe thoracic and upper abdominal trauma. Unlike the post aorta-coronary bypass patients, a youngster with arrhythmias following chest injury is not necessarily headed for low cardiac output. Drs. Wechsler and Alexander, in a court-side consultation, suggested using Swan-Ganz catheters and cardiac output measurements using thermodilution, just as we occasionally do with sick post coronary bypass patients.

Our experience with Technetium, as described by Ehrenhaft, is limited, but we have been surprised to find normal scans when we

thought we should have seen signs of myocardial injury.

A syndrome is capricious only so long as the observer is ignorant. Dr. Drapanas and his colleagues at Tulane have a knack for identifying areas of ignorance and controversy in the management of the injured and helping to bring reason to bear.

DR. WATTS R. WEBB (Syracuse, New York): Myocardial contusion represents, in essence, a myocardial infarction. It has a little different pattern; and thereby doesn't present the typical changes on electrocardiogram of the usual infarction.

The tipoff that we usually note—and this, obviously, is not a new observation—is that these patients have a tachycardia which is completely out of keeping with the degree of trauma or blood loss or sepsis or other things that might be present. The diagnosis depends also on the EKG, and I think of great importance are the serial enzymes, particularly the level of the CPK, because if the creatine phosphokinase goes up very high, then you know that you have a very severe myocardial infarction.

We have had only one opportunity with these patients who go into pump failure. Just like others who have myocardial infarction, they should be handled with intraaortic balloon pumping. This should be very effective, because, in essence, in virtually every instance this is a reversible lesion.

We'd like to report one other case of coronary occlusion secondary to

chest trauma. This was in a 26-year-old campus patrolman, who was struck in the precordium by a full beer can during one of the campus riots about four years ago. He survived the initial infarction that he had, and at a later date we were able to revascularize the anterior descending coronary that had obviously been occluded as a result of the trauma.

DR. JAMES W. JONES (Closing discussion): Dr. Mattox's first question pertains to a very important medicolegal problem. Were these injuries precipitated by stress in a previously atherosclerotic patient, or were the injuries primarily from direct myocardial trauma? This study did not attempt to resolve that question because most of our patients were young and had no previous history of heart disease. It is a question that has been discussed for years in the literature and I don't know that anyone has ever developed a truly useful antemortem method of determination in the elderly trauma victim.

His second question is an important one. When you diagnose this entity by electrocardiography, you are diagnosing a bioelectric abnormality. Exact correlation of the electrocardiographic changes with the pathological entity is not critical, because in this study we are only interested in prognostic implications of a clinical syndrome.

We agree wholeheartedly with the speakers who remarked on the relative absence of chest wall injury in these patients, as pertains to rib fractures and sternal fractures. In our series, there was no correlation between rib or sternal fractures and the post injury clinical course.

Management of Thoracic Outlet Syndrome

W. ANDREW DALE, M.D., MALCOLM R. LEWIS, M.D.

This overall management program for thoracic outlet compression syndrome is based upon experience with 153 extremities in 149 patients and the results of others. The following conclusions are documented and discussed. 1) Diagnosis is based chiefly upon history; physical signs are inconstant and often absent. 2) Major vascular problems are unusual; angiography is not always necessary. 3) Electromyography is not always critical but does aid in diagnosis of carpal tunnel syndrome. 4) Non-operative treatment relieves most patients; operative decompression is indicated for a minority. 5) Transaxillary first rib resection, with removal of cervical rib is the best operation. 6) Carpal tunnel decompression should be done concomitantly when needed. 7) Operation is relatively safe.

DURING the past 7 years an integrated concept of management of thoracic outlet compression syndrome has been developing which produces good to excellent results in most patients. Numerous articles and increasing numbers of operations attest to widespread interest in the problem which 20 years ago was barely known. There are still unanswered questions relating to pathogenesis, misunderstanding of the clinical syndrome and only partial agreement upon indications and techniques of management. This retrospective study of 153 extremities in 149 patients is discussed in the light of our experience and the background of the reports of others and is particularly directed toward the continuing development of a rational method of overall management.

Our experience with 153 upper extremities in 149 patients (1966-74) is summarized in Tables 1-5. Specifically excluded are 15 patients who eventually proved to have carpal tunnel syndrome alone. Follow-up range D from a month to 8 years.

Surgeons do not usually discuss cases which do not require operation but since most people with thoracic outlet syndrome fall into the non-surgical category they are included here.

From the Department of Surgery, Vanderbilt University School of Medicine, St. Thomas Hospital and Baptist Hospital, Nashville, Tennessee

Present Clinical Management

Patients suspected of thoracic outlet syndrome are initially examined with emphasis upon the history of pain, paresthesias, edema and motor dysfunction (Fig. 1). Known aggravating factors such as injury, rib anomalies, unusual positions as well as general health factors are noted. Examination is directed toward tenderness, masses and bruits in the neck along with pain or pulse cut-off by arm position change. Sensory and motor tests, peripheral pulses, and temperature examination are also done.

If the diagnosis of thoracic outlet syndrome (TOS) seems likely, shoulder girdle strengthening exercises (Table 6) are explained and the patient is asked to follow this program regularly for three weeks. Tranquilizers or sedatives to interrupt the cycle of nervous and muscular tension are often prescribed along with warm tub baths to promote relaxation of the muscles of the neck and shoulder girdle. Occasional patients are made worse by exercises and are warned to discontinue should this occur.

During this three week period electromyography is done, the cervical spine and chest are x-rayed for anomalies, and a stress electrocardiogram and cardiac consultation are obtained if there is a component of chest pain.

At the next office visit the results of exercise and the studies are evaluated and the patient either continued on nonoperative therapy, referred for cardiac therapy, or scheduled for carpal ligament lysis. If symptoms are not relieved there is given a week trial of cervical halter traction as an out-patient in the Physical Therapy Department. This does not help thoracic outlet syndrome but usually benefits cervical disk pressure and is therefore of differential diagnostic benefit.

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1974, Boca Raton, Florida.

TABLE 1. 153 Extremities of 149 Patients

	Non-operated	Operated	Total
Male	29	14	43
Female	68	42	110
Age:			
< 20	4	1	5
21-30	22	9	31
31-40	21	24	45
41-50	30	14	44
51-60	15	5	20
> 60	5	1	6
Total	97	56	153

Should severe symptoms continue, hospitalization is arranged. Two-position subclavian angiograms and in some cases phlebograms are obtained. Neurosurgical consultation is requested and myelography if indicated.

If thoracic outlet syndrome continues as the diagnosis the patient is offered (but not urged) brachial plexus decompression by the appropriate procedure and is advised of the expected chance of relief along with that of failure. By this time it is believed that other causes of the symptoms have been ruled out and that nonoperative therapy has been unsuccessful; most patients now request operation.

Operations are therefore reserved for patients who continue to have symptoms and do not respond to lesser measures over a period of time. Occasionally, the symptoms may be so acute that immediate operative decompression is warranted. This occurs when pain of a severe degree necessitates opiates, or if the vascular structures are severely involved or become thrombosed.

Method

The best method to decompress the neurovascular bundle is removal of the first rib along with cervical rib if that is present. At least 4 approaches to the first rib are possible but the transaxillary is easiest and produces less pain and fewer complications once the technique is mastered.

The patient is placed in the lateral thoracotomy position and the table later rolled back about 30-40°. The arm is sterilely draped into the field to allow traction upon it (Fig. 2).

TABLE 2. Clinical Syndrome in 153 Extremities

	Non-operated	Operated	Total
History			
pain	97	56	153 (100%)
paresthesia	63	26	89 (58%)
motor weakness	17	18	35 (23%)
edema	14	11	25 (16%)
Examination			
pain in AER	14	12	26 (17%)
pulse cut-off	21	20	41 (27%)

TABLE 3. Laboratory Findings

	Non-operated	Operated	Total
Plain x-ray:			
cervical rib	5	11	16 (12%)
1st rib anomaly	0	1	(1%)
Anteragram:			
abnormal	2 of 5 (40%)	13 of 29 (45%)	15 of 34 (44%)
Phlebogram:			
abnormal	0 of 5 (0%)	6 of 8 (75%)	6 of 13 (46%)
Electromyogram:			
shoulder abnormality	1	4	5
elbow abnormality	1	0	1
wrist abnormality	3	5	8
no abnormality	8	15	23
(40% of 38 were abnormal)			

A transverse incision is made just below the axillary hairline and dissection from pectoralis major to latissimus dorsi muscle is deepened to the rib cage and then upward into the axilla until the vessels are encountered as they pass over the superior edge of the first rib.

The key to a safe and efficient operation is the exposure provided by elevation of the shoulder girdle by upward traction by an assistant. Several methods of traction have been tried, including attachment of the arm to a movable pole for elevation and similar attachment to an overhead orthopedic traction device. The best exposure is obtained by a vigorous assistant holding the wrist and forearm in a hammerlock¹⁰ and pulling upward by leaning back to lift the neurovascular bundle off the first rib. Assistants may be alternated at 10 minute intervals. Approximately 20 minutes of exposure is currently required for careful dissection and removal of the first rib.*

The sensory nerve crossing the axillary operative field is recognized and divided since an area of anesthesia on the medial upper arm is preferable to postoperative neuritic pain.

The anterior scalene muscle is isolated at its attachment to the superior border of the first rib and divided. The first rib is dissected extraperiosteally to avoid regeneration. The dissection is carried out not only by curved, sharp periosteal elevators and scissors but also by the operator's finger which is more sensitive than steel instruments and is used wherever possible. The long thoracic nerve lying on the lateral rib cage is avoided to prevent scapular "winging" if injured. The rib is resected posteriorly near the transverse process of the vertebra

*We have personally participated in this retraction and recommend that every surgeon proposing to do this procedure should familiarize himself with the problem similarly.

THORACIC OUTLET SYNDROME

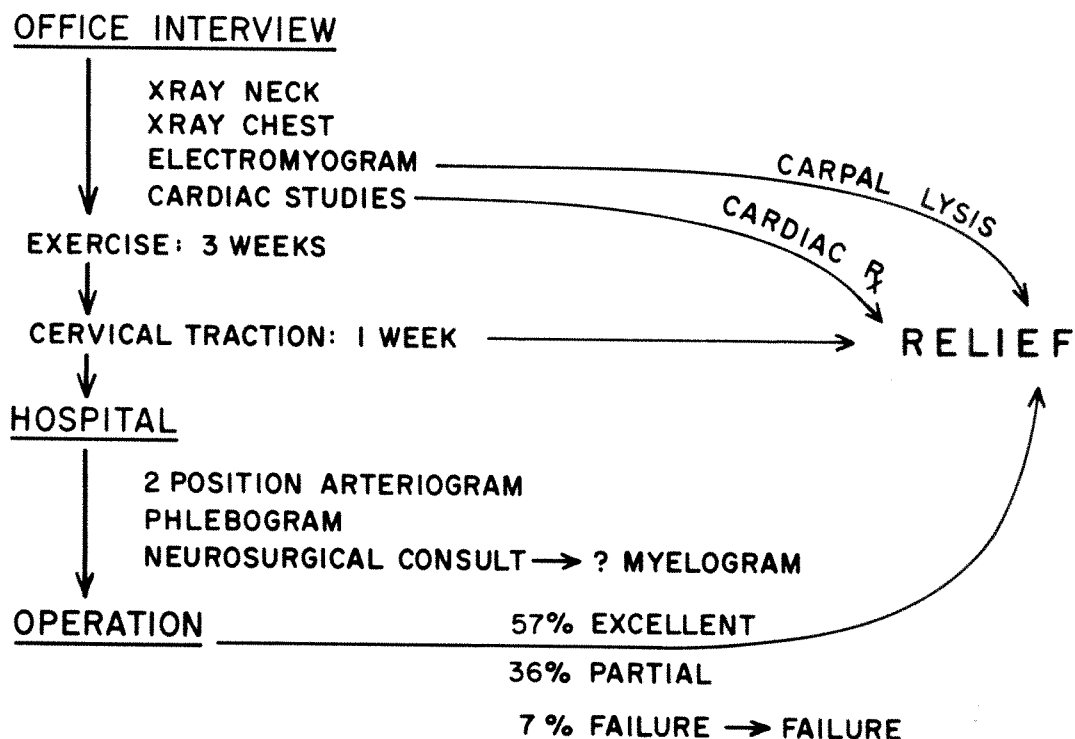


FIG. 1. Flow pattern for current management of patients with thoracic outlet syndrome.

and anteriorly at its junction with the rib cartilage (Fig. 3). During the rib resection a special brachial plexus shield is placed between the rib cutter and the brachial plexus to protect it. Considerable help has been available recently from a newly developed extra-long double-action, thin-beaked rib rongeur which is superior to others which were previously available.*

Resection of the rib posteriorly is more important than at its anterior junction with the cartilage. The operator looks to see if the brachial plexus impinges upon the cut end of the rib, feels for rough spicules, and lowers the arm to the side while two fingers are placed in the resected rib bed to be certain that decompression is adequate.

If the underlying pleura has been opened the resultant pneumothorax is easily managed by placing a small catheter and sucking on this as it is withdrawn after the wound is closed in layers. If the pleura has not been entered a small Penrose drain is left in place for 24 hours. This is not placed if the pleura has not been opened for fear of direct communication and resultant pneumothorax.

The operation requires 40 to 90 minutes, being more difficult in heavily muscled patients. Blood loss is minimal and no transfusion has ever been needed.

Two points are stressed in postoperative care. First, a

semi-upright chest film is made in the Recovery Room to be certain that a pneumothorax is not overlooked. Secondly, the patient is encouraged to begin full overhead arm motion on the day following surgery and the Physical Therapy Department is enlisted to aid this maneuver should it prove necessary.

A cervical rib is often accessible through the axillary approach after removal of the first rib (Fig. 4). If there is difficulty or if the patient is large or obese a secondary supraclavicular incision may be used (one in this series).*

Illustrative Case Reports

Case 1. A 44-year-old woman had vague pain in her right arm near the elbow with weakness of grip with incoordination. There were no positive physical findings nor x-ray abnormalities. Electromyography showed delay in nerve conduction both at the elbow and wrist.

Exercises did not relieve the symptoms. Transaxillary first rib resection was performed with concomitant carpal tunnel release. Twenty-one months after operation she had no pain but said that her right upper extremity was so weak that she was "hardly able to work." There was some demonstrable weakness in the grip on that side.

Comment. Should this patient be classified as an excellent result or as improvement? There are a combination

*This rib rongeur is available from Codman and Shurtleff, Pacella Drive, Randolph, Mass 02268.

*The 1971 description of operative technique for cervical rib removed by Clarence J. Schein is excellent.³⁷

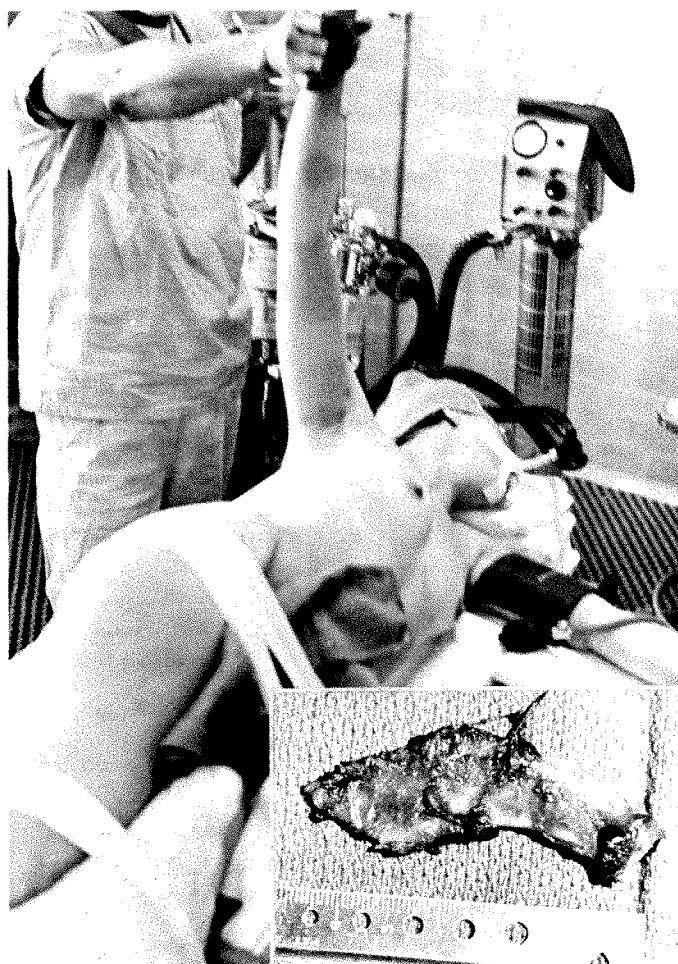


FIG. 2. Position for transaxillary resection of first rib. Arm is prepared and draped into the field. Inset: Excised rib.

of factors which may suggest to the patient that she has good reason to avoid work at a boring job. She was classified as "improved."

Case 2. A 33-year-old woman had transaxillary resection of the first rib for relief of shoulder and arm pain of 6 months duration associated with paresthesias in the left shoulder and arm. The preoperative pulse cut-off during elevation was changed and she obtained relief. The

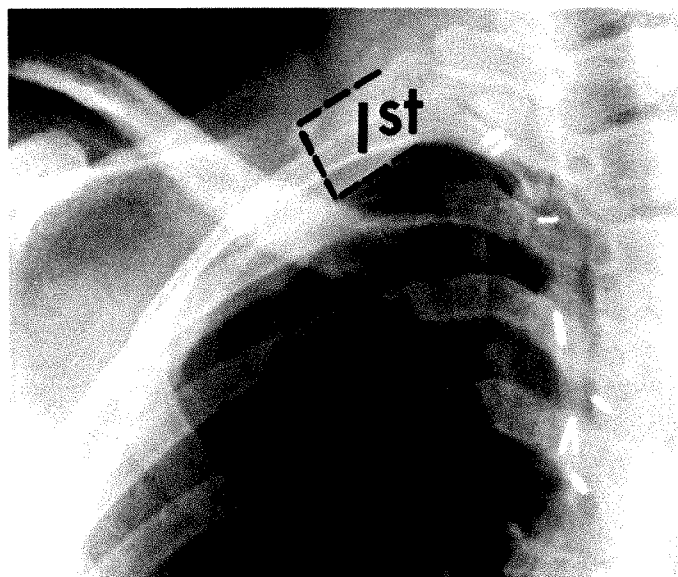


FIG. 3A. Postoperative appearance after first rib resection. Clips were placed during concomitant sympathectomy.

preoperative arteriogram had shown narrowing. Electromyography was normal.

Nine months later there was recurrence of pain in the left lateral neck. Electromyography was again negative. Cervical myelography was negative. A previously recognized cervical rib on the contralateral (asymptomatic) side was still present and raised a question as to whether there might be a fibrous band on the painful side although x-ray again did not show any cervical rib or other anomaly of the bony cage.

Thirteen months following the original operation the left neck was explored through a supraclavicular approach to be certain that there was no soft tissue band compressing the brachial plexus. Nothing was found. The medial half of the clavicle was resected and an additional amount of anterior scalene muscle was removed. She again had relief of pain.

Two years later she was rehospitalized for recurrence of pain in the left neck and shoulder. There were no positive findings and she was treated symptomatically.

Comment. This illustrates inability of her internist, a neurosurgeon and ourselves to obtain complete relief despite two operative procedures. The patient is classed as improved. Her symptoms are inconsistent, but it is uncertain whether operation had any specific decompressive effect.

Results

There was some relief of symptoms by one method or another in 97% of the extremities (Table 4).

Among those having surgery, 93% obtained complete or partial relief while 7% were failures in that symptoms were unchanged. None were made worse.

There were no deaths. Complications are listed in

TABLE 4. Results of 56 Operations in 54 Patients

	Complete Relief	Improved	Failure
49 Transaxillary 1st rib resect.	20	14	2
+ clavicle resect.	2	—	—
+ cervical rib resect.	3	1	—
+ carpal lysis	4	2	1
(subtotal: 1st rib removal) (29 = 60%)		(17 = 35%)	(3 = 6%)
4 Resection cervical rib + scalenectomy	1	3	—
3 Scalenectomy only	2	—	1
Total	32 (57%)	20 (36%)	4 (7%)

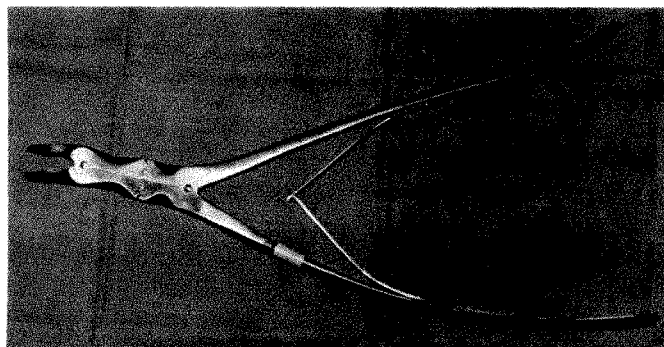


FIG. 3B. Extra long double action rongeur has thin beak for removal of posterior end of rib.

Table 5. All were temporary except for one patient who had a permanent limitation of elevation of the shoulder following inability to mobilize the shoulder properly postoperatively.

Discussion

The twisting road which has led to our present understanding of thoracic outlet syndrome began over a hundred years ago when the first clinical diagnoses were recorded and an early attempt was made to remove the first rib by Coote in 1861.¹² Prominent surgeons successively became interested in the problem, and in 1905, John B. Murphy of Chicago resected a cervical rib which had produced a subclavian aneurysm.²² By 1916 Halsted was able to find records of 716 patients with cervical ribs; he conducted experiments to determine the cause of the occasional aneurysm of the overlying subclavian artery.¹³

Telford and Stopford demonstrated how the brachial plexus and subclavian artery could be compressed by the first thoracic rib and reported 6 patients who were relieved of symptoms following its resection.³⁸ Adson, in 1927, reviewed the subject extensively and introduced his clinical test.¹ The role of the scalene anticus muscle in neurovascular compression was developed further by Naffziger and Grant²³ and by Ochsner, Gage and DeBakey in 1935²⁵ and succeeding years saw other compression syndromes described. Peet and associates, in 1956, suggested that all of these compression syndromes might be termed thoracic outlet syndrome;²⁶ this term was later modified by Rob and Standeven to thoracic outlet compression syndrome, which includes all syn-

TABLE 5. *Complications*

Deaths: 0	Infections: 0
Temporary long thoracic nerve injury	2
Acute bursitis of shoulder	2
Stiff shoulder	2
Pneumothorax requiring aspiration in recovery room	2
Wound hematoma	1

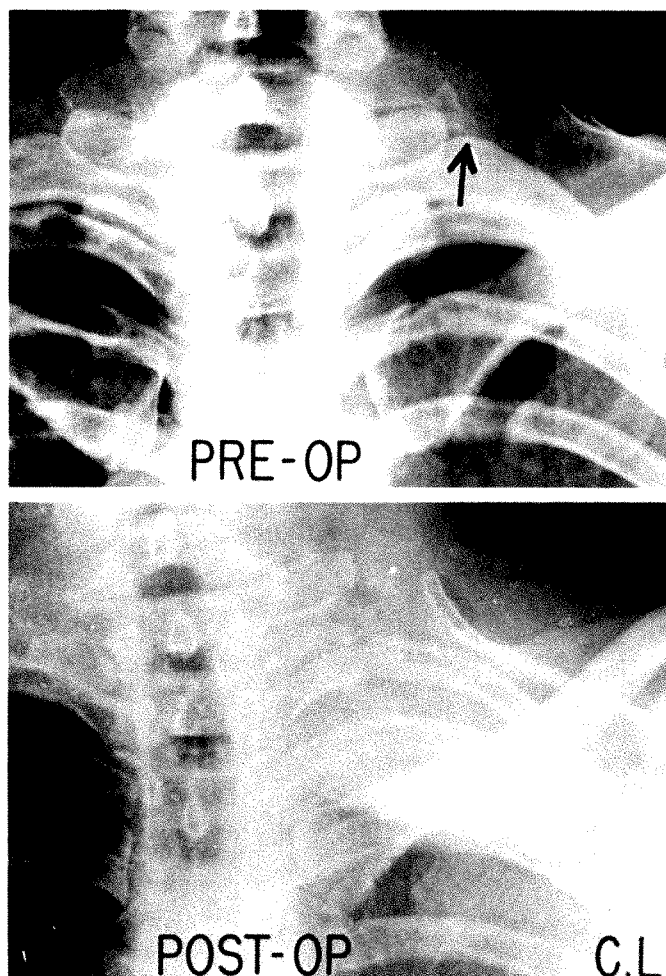


FIG. 4. Cervical rib at arrow was removed along with first rib by transaxillary approach.

dromes of compression of the neurovascular structures of the upper extremities.²⁹ The term "neurovascular compression syndromes of the shoulder girdle" used by Rosati and Lord³⁴ is more correct terminology but is bulky and since "thoracic outlet syndrome" has now been generally accepted (even by these authors) it will be used here.

The significant failure rate of scalenectomy alone led to efforts to achieve greater decompression. McCleery and associates, in 1951, added removal of the costocoracoid membrane and subclavian muscle² while Rosati and Lord, in 1961, emphasized claviclectomy.³ Resections of the first rib had been reported earlier⁴ and in 1962, Clagett redirected attention to this when he reported his good results after resection of the first rib *via* the posterior approach.⁵ Ferguson, Buford and Roper confirmed this in 12 other patients¹¹ and Clagett later increased his reported series to 44 successful first rib resections.¹⁸

Resection of the first rib *via* the axillary approach was described in 1966 by Roos³¹ whose series has been enlarged to over 450.³² This route allows removal of the rib without cutting muscles and has been productive of good

TABLE 6. *Shoulder-Girdle Exercises for Thoracic-Outlet Syndrome**

At the beginning, each exercise is done 10 times in succession twice a day. As the shoulders and neck gain strength, the number of times each exercise is done consecutively can be increased. The six exercises follow:

1. Stand erect with the arms at the sides, holding in each hand a 2-pound weight (sandbags, or bottles, jars or sacks filled with sand). (a) Shrug the shoulders forward and upward. (b) Relax. (c) Shrug the shoulders backward and upward. (d) Relax. (e) Shrug the shoulders upward. (f) Relax and repeat.
2. Stand erect with the arms out straight from the sides at shoulder level; hold a 2-pound weight in each hand (palms should be down). (a) Raise the arms sideways and up until the backs of the hands meet above the head (keep elbows straight). (b) Relax and repeat. Note: As strength improves and exercises 1 and 2 become easier, weights should be made heavier; increase to 5 and later to 10 pounds.
3. Stand facing a corner of the room with one hand on each wall, arms at shoulder level, palms forward, elbows bent and abdominal muscles contracted. (a) Slowly let the upper part of the trunk lean forward and press to the chest into the corner. Inhale as the body leans forward. (b) Return to the original position by pushing out with the hands. Exhale with this movement.
4. Stand erect with the arms at the sides. (a) Bending the neck to the left, attempt to touch the left ear to the left shoulder without shrugging the shoulder. (b) Bending the neck to the right, attempt to touch the right ear to the right shoulder without shrugging the shoulder. (c) Relax and repeat.
5. Lie face down with the hands clasped behind the back. (a) Raise the head and chest from the floor as high as possible while pulling the shoulders backward and the chin in. Hold this position for a count of three. Inhale as the chest is raised. (b) Exhale and return to the original position. (c) Repeat.
6. Lie down on the back with arms at the sides, with a rolled towel or small pillow under the upper part of the back between the shoulder blades and no pillow under the head. (a) Inhale slowly and raise the arms upward and backward overhead. (b) Exhale and lower the arms to the sides. (c) Repeat 5 to 20 times.

*From Fairbairn, Juergens, Spittell, *Peripheral Vascular Diseases*, W. B. Saunders, Philadelphia 1972, Page 473.

results with few complications. Excision of the first thoracic rib removes the floor of the compression compartment and allows the neurovascular bundle to drop downward away from the overlying and enclosing structures.

Pathogenesis. The narrow space composed of firm or rigid structures through which course the nerves and vessels from the neck to the axilla easily causes pressure. The addition of congenital anomalies of ribs and muscles compounds this, as does any unusual position which is persistent, such as hyperabduction at work or during sleep, an injury, degenerative changes, and muscle spasm. Harold C. Urschel's diagram (Fig. 5) appears to be a reasonable explanation of how pressure occurs.⁴⁰

Lord and Rosati have enumerated 5 factors which may contribute to pressure, namely: 1) congenital anomalies,

2) static size or shape of compressing structures, 3) dynamic changes with motion, 4) trauma, including fractures and "whiplash," and 5) the aging processes of arteriosclerosis and muscle atrophy.²⁰

The actual reason why some people develop pressure symptoms while most do not is unclear. The common occurrence in middle age (78% were 21-50-years-old in our series) and in women (72%) has suggested that muscle atrophy combined with increasing weight accounts for many instances. However, this explanation collapses with examination since age and obesity should cause even further loss of muscle tone, yet the incidence of symptoms diminishes as age advances.

Cervical rib is said to occur in 1% of the population and to be symptomatic in 10% of instances. Twelve per cent of our patients had cervical ribs and another one had an anomaly of the first rib. This crowding of the space understandably causes compression.

Thoracic outlet symptoms not infrequently begin after injury, automobile whiplash accidents being the most common form in the United States. Sanders, Monsour and Baer noted that 52% of their 58 patients featured this,³⁵ while Roos and Owens reported it in 34% of 138 patients.³³ The actual incidence is difficult to obtain since close questioning often brings out some memory of a neck or shoulder injury, in these patients which may be overlooked.

The following conclusions are based upon review of our patients as well as the reports of others and are offered with knowledge that full documentation of these ideas is not possible and that some may prove to be erroneous.

1. *Diagnosis is more dependent upon history than examination.* Some form of pain is invariable. It is often

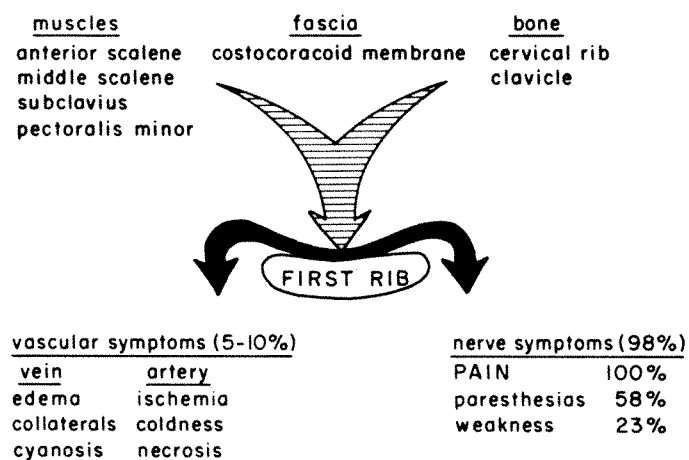


FIG. 5. Thoracic outlet syndrome. Causes of pressure upon brachial plexus, modified from Urschel.³⁹

vague and the patient finds localization difficult. It is not pin-pointed to the shoulder or elbow and may lead the inexperienced clinician to conclude that it is not real. The pain is due to nerve pressure and not to ischemia as has been thought in the past.

Anterior chest pain may also occur. This has been termed pseudo-angina by Urschel and associates who differentiated brachial plexus pressure as it cause in 44 patients. Another 13 patients had both thoracic outlet syndrome and angina due to coronary arterial disease. They used coronary arteriography and electromyography to differentiate.⁴²

Paresthesias are common (58% here) and more often involves the ulnar distribution, but also may be general. Motor incoordination (23%) may be manifest by dropping objects, or weakness of grip. Edema (16%) in this group was chiefly by history of enlarged finers and hands and was not usually pitting and demonstrable.

Lack of postive physical findings was noted. Only a minority (17%) had pain when the arm was elevated and externally rotated. The Adson test for pulse cut-off was similarly disappointing, frequently resulting in numerous false positives in asymptomatic patients.

The subjective nature of pain along with the paucity of objective findings often leads to uncertainly in diagnosis. Restriction of definitive treatment to those with a sure diagnosis will fail to provide available relief of pain to some patients while acceptance for surgery on the basis of loose indications leads to confusions and unnecessary treatment.

A large number of differential diagnoses may be listed but the problem essentially comes down to three questions (Table 7). First, is pain of organic origin? Second, are the symptoms typical of nerve pressure, that is, pain which is widespread and poorly localized, or is the pain in a joint or tendon with local manifestations?

The final question is whether the nerve compression exists at the level of exit of the nerves from the cervical vertebra, at the thoracic outlet, at the elbow or at the wrist. All of these pressure points occur, may co-exist and tend to be confuses. In this series no instance of compression at the elbow has been recognized, but 7 of the 59 patients undergoing operation also had lysis of the transverse carpal ligament at the wrist and an additional

15 patients who originally were thought to have thoracic outlet syndrome were operated upon for carpal tunnel syndrome as the proper diagnosis (outside of this series).

Symptoms of hand ischemia (Raynaud's phenomenon, coldness, or ulceration) are not ordinarily produced by thoracic outlet syndrome but by Raynaud's disease or Raynaud's phenomenon secondary to other problems. In the older literature it is commonly stated that Raynaud's phenomenon may accompany thoracic outlet syndrome but we have not observed such (although we see a good many patients with hand and finger ischemia due to other causes).⁹ Brachial angiography is the key examination for differential diagnosis in this situation.

2. *Major vascular problems are unusual; angiography is not always necessary.* Vascular signs have been thought common but our experience denies this since only one arterial and three venous problems attributable to thoracic outlet pressure have occurred in the 8 year time period of this series.

The arterial problem⁸ consisted of axillary thrombosis and required a graft as well as distal decompression (Fig. 6).

The three venous cases of phlegmasia cerulea dolens were treated by intravenous heparin. Only one of the three required venous thrombectomy (Fig. 7).

The small number of serious vascular complications is attested by Roos' incidence of 6%,³² Sanders of 12%,³⁵ and Urschel's one arterial and 14 venous problems among 400 patients (4%).⁴¹ Judy and Heymann in 1972 reported only 53 major vascular complications in the English literature¹⁵ beyond the 29 earlier ones of Schein, Haimovici and Young.³⁷

The arterial problems which do occur are generally associated with cervical ribs or other bony anomalies at the thoracic outlet. As long ago as 1939 Eden found only a single such case without a bone abnormality among a total of 42.¹⁰ More recently Raphael, Moazzez and Offen reaffirmed this in connection with 7 cases²⁸ and Bland and Connor reported 6 arterial problems associated with cervical rib or first rib abnormalities among their 40 patients operated upon for thoracic outlet syndrome.³ Our patient with an arterial problem had a cervical rib. It is therefore not likely that a vascular complication will occur in the absence of cervical rib or anomalous first rib.

This implies that angiography should be done when such bony anomalies are present. The results of two-position angiography in other patients is less rewarding. Among 34 arteriograms in this series positive findings were limited to 44% of these angiograms. The changes consisted of minor degrees of stenosis due to external compression, often accompanied by a small amount of post-stenotic dilatation (Figs. 7 and 8). No aneurysms nor thromboses were discovered except for the one noted above. This is a considerably smaller percentage than the 70% of 158 patients studied by Land.¹⁷ The results of routine angiography have therefore been disappointing

TABLE 7. *Differential Diagnosis*

-
1. Pain
 - (a) is it of organic origin?
 - (b) is it due to nerve pressure?
 - (c) is the pressure; at the vertebral column & thoracic outlet? Elbow? wrist?
 2. Common lesions to be ruled out:
 - (a) cervical root pressure by disk; arthritis
 - (b) shoulder "bursitis"
 - (c) occlusion of arteries of wrist or hand
 - (d) carpal tunnel syndrome
-

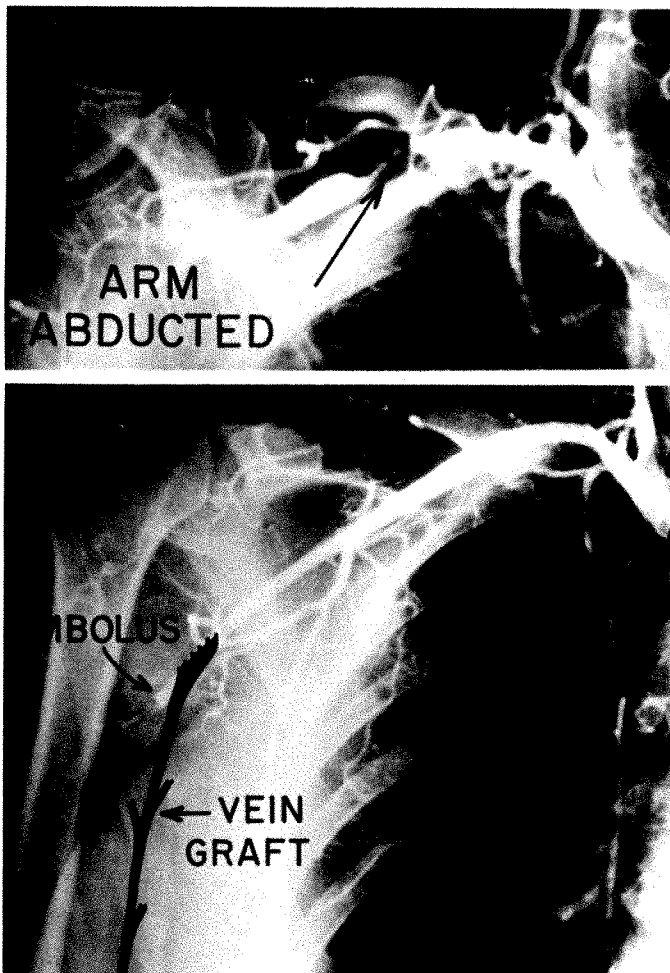


FIG. 6. (Top) The axillary artery is sharply compressed at the arrow when the upper extremity is elevated and abducted and this resulted in distal embolism. (Bottom) The axillary artery appears normal with the arm in the dependent position. The vein graft was used to bypass the old embolism and secondary thrombosis of the brachial artery. First rib resection and claviculectomy were also done.

and this test did not particularly aid in differential diagnosis or treatment. We now believe it should be used chiefly for patients whose history or physical examination casts suspicion upon the artery or when a bone abnormality is present and that it is not useful for the majority of patients with thoracic outlet syndrome whose symptoms are due to nerve pressure. Eight of our "complete relief" patients and eight of our "improved" patients had negative two-position arteriograms. *Had we insisted upon positive angiographic findings these patients would have been denied operative relief.*

Approximately half of the 11 phlebographic examinations showed an abnormality. Phlebography, however, was limited to patients with edema or venous collateralization around the shoulder girdle since even the positive phlebograms did not alter our method or management. Phlebography is as often confusing as it is helpful and we now rarely use it.

3. *Electromyography is not often critical but does aid*

diagnosis of carpal tunnel syndrome. The 1968 report of Urschel, Paulson and McNamara that pressure slowed nerve conduction with postoperative reversal in 17 patients suggested this might become a critical objective test.³⁹ Krogness studied 5 patients before and after scalenectomy⁴ and first rib resection¹ and reported similar findings.¹⁶ The electromyogram has not yet been widely accepted; Roos for example has stated that it was unrewarding in his work-up of 1700 patients. Disagreement between its advocates in regard to the effects of position is also noted.

In the latter part of this series there were 38 patients who had electromyograms; only 40% were abnormal. Positive findings at the shoulder level were infrequent and the chief value of electromyography in our hands is to furnish information regarding never pressure at the wrist, which agrees with Lord's viewpoint.¹⁹

We are unable to explain the difference between our experience and that of the advocates of electromyography. But whatever the cause, we cannot rely upon it as a practical objective test for thoracic outlet syndrome at present.

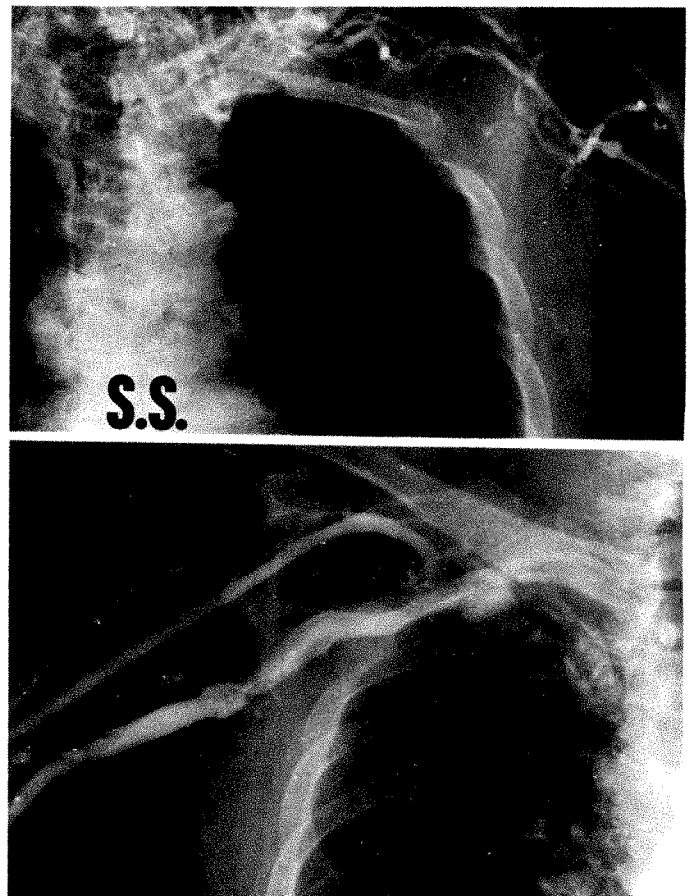


FIG. 7. (Top) Phlebogram shows thrombosis of left subclavian and axillary veins with phlegmasia cerulea dolens. (Bottom) Normal right veins. Heparin treatment was successful.

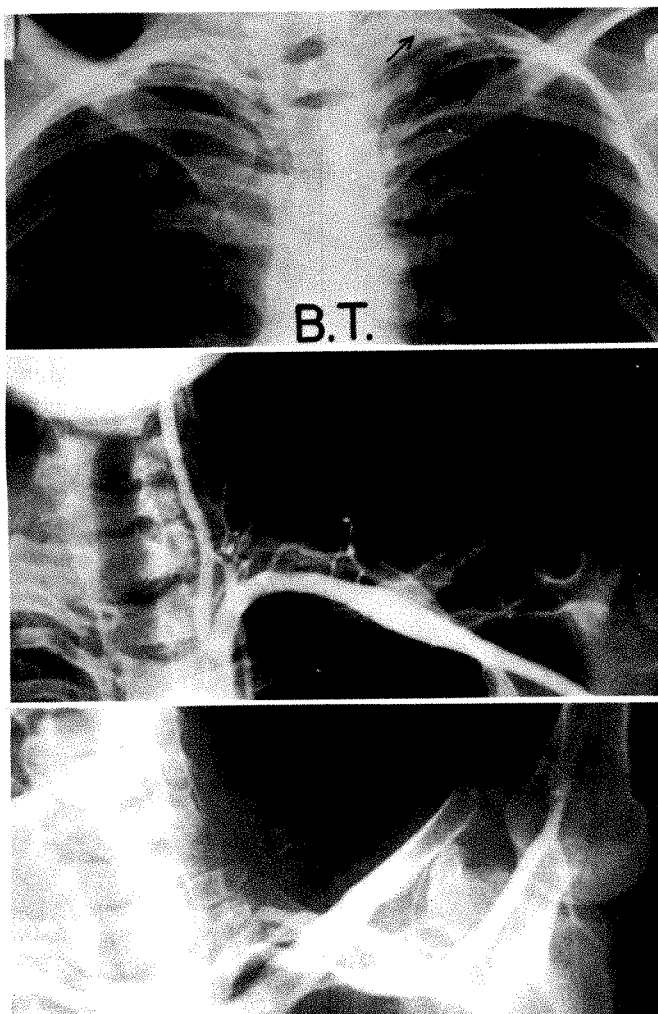


FIG. 8. (Top) Cervical rib at arrows; (Bottom) Slight stenosis and post-stenotic dilatation of subclavian artery.

4. *Non-operative treatment relieves most patients; operative decompression is indicated for a minority.* Most writers do not emphasize the large number of less severe cases which respond to non-operative treatment. Sixty-three per cent of our patients did well with exercises and temporary drug relief while only a minority (37%) required surgery.

The 7% operative failure rate was not surprising in view of the difficulty of differential diagnosis. The 36% who obtained partial but not complete relief do concern us. These patients were relieved of most of their symptoms but still did not have a perfectly normal arm. Either the reports of others are overly optimistic or their followups are poor or our treatment is not as good as theirs. Our own ideas have required modification after careful retrospective examination of results and we suspect that statements of 100% good results by others are not critical. Either way we have learned not to promise more than can be delivered to the patient. Fortunately the mortality rate is nil and complications are few and temporary.

5. *Transaxillary first rib resection, with removal of cervical rib when present is the best operation.* The most reliable decompression of the brachial plexus is by removal of the floor of the compression area by resection of the first rib. The transaxillary approach of Roos has the advantage of simplicity, directness, no muscles are cut and convalescence is rapid. It is a deep exposure and requires the development of some experience. Once this is learned it is easier than the posterior approach, less dangerous to the artery than the supraclavicular¹² and more direct than the subclavicular route.²⁴

A cervical rib can usually be removed through the axilla after the first rib is out. If there is undue difficulty a secondary supraclavicular incision may be used. Removal of the cervical rib alone may not completely relieve symptoms and first rib resection should therefore be done simultaneously.

Illustrative Case Report

Case 3. A 44-year-old woman underwent removal of a cervical rib 3 years previously with relief of anterior neck and shoulder pain but continuation of posterior arm pain radiating down into the hand. Angiography showed no vascular constriction, although the pulse was absent with the arm elevated. (The contralateral asymptomatic arm

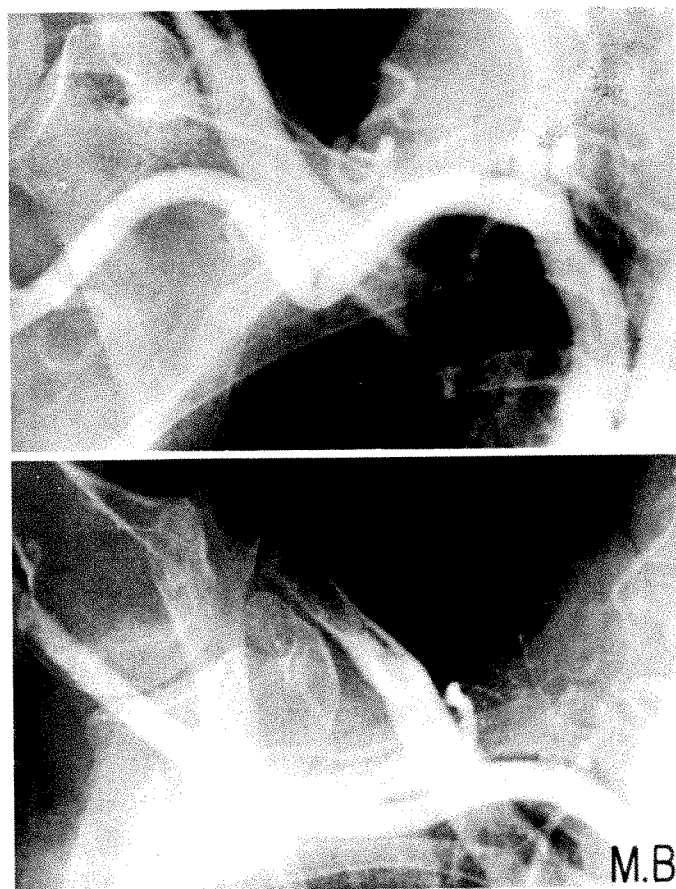


FIG. 9. (Top) Unusual finding of kink in subclavian artery, arm at side. (Bottom) The artery straightens to normal with arm elevated.

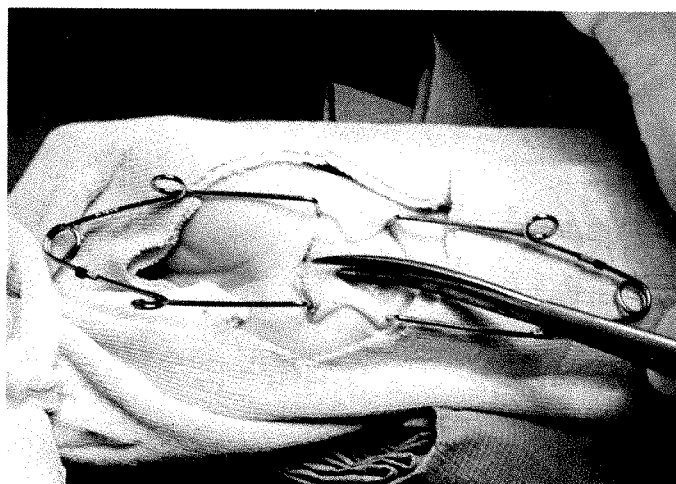


FIG. 10. Cutting the transverse carpal ligament at wrist through a Z-incision to decompress the median nerve.

also had similar pulse cut-off upon elevation.) Secondary operation consisted of supraclavicular removal of the medial half of the clavicle along with the subclavius muscle, a remnant of the scalene muscle and the first rib. Her postoperative course was uneventful and she was asymptomatic at 9 months.

Comment. It was necessary to add first rib resection to removal of the cervical rib to effect complete relief.

Should sympathectomy be required, it may be easily done by a transpleural approach *via* the third interspace using the same incision.

6. *Carpal tunnel decompression should be done at the same time when needed.* If there is any question about lysis of the transverse carpal ligament it should be done at the same time to avoid the necessity for a second hospitalization for the wrist operation.

Lord emphasized the concomitant carpal tunnel syndrome in his report on 123 patients. Seventeen had concomitant carpal tunnel syndrome and 5 required two separate operations (thoracic outlet decompression plus later section of the transverse carpal ligament at the wrist).¹⁹ Two patients in our series had accompanying carpal tunnel syndrome and required later secondary operative relief to produce complete cure. An example is a 44-year-old woman with a 4 year history of numbness in the hand which awakened her at night and interfered with her secretarial work. Some edema was also noticed and led to resection of the first rib for thoracic outlet syndrome. Shortly thereafter pain recurred. It was relieved by section of the transverse carpal ligament.

7. *Operation is relatively safe.* Absence of mortality is notable in this series as well as other series^{4,11,14,20,32,35,41} and complications are few and temporary. This allows operation to be recommended when needed. It also will allow a non-critical surgeon to advocate surgery for some patients who do not really require this, but the com-

plaints of "failed" patients who continue to complain afterwards will eventually discourage this attitude.

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DISCUSSION

DR. JERE W. LORD, JR. (New York): My comments, instead of agreeing with everything that Dr. Dale says in other areas, is somewhat critical, although not of his approach to this problem. His workup is probably the most thorough of any surgeon in this country. The patients are studied carefully, are not rushed into an operation, but are seen by consultants, have electromyographic studies, and many other tests. What really disturbs me is that only 57% obtained excellent results and 43% were either fair or poor. If we were able to diagnose these patients accurately, then we should have a higher percentage of excellent results.

The second feature is that Dr. Dale, who is an outstanding vascular surgeon, observed that only 5% of the patients studied had arterial and venous problems. All of the other symptoms were on a neurological basis. Roos has operated upon more than 400 patients and of these only 6% were vascular; 94% were neurological. To have 95% of the patients operated upon for neurological symptoms only is a worrisome thing to me. I remember in the late 30s and early 40s, when section of the scalenus anticus muscle was a popular procedure and was approved of highly by some of the important members of this Association. Later the procedure fell into disrepute around the nation for so many poor results were noted. I am deeply concerned that the excellent operative technique of Roos and Owens of transaxillary resection of the first rib may also in another five or ten years all into disfavor not because the technique is not excellent but because the selection of patients is so difficult.

My colleagues and I operate only upon some five to six patients a year for the thoracic outlet syndrome and most of these are on an arterial or venous basis.

DR. HILARY H. TIMMIS (Royal Oak, Michigan): I would like to congratulate Dr. Dale on the clinical review of his cases of thoracic outlet syndrome and describe a few observations we have derived from the surgical management of 175 patients with this problem.

First of all, let me state emphatically that the vast majority of these patients have neurological, rather than vascular symptoms. The response to treatment depends to a great extent on what precipitated the syndrome. It would appear that many have an anatomic predisposition to it, and with trauma, sometimes relatively minor, they begin to have chronic pain.

Hyperextension injuries are especially pernicious and we suspect result in injury to the scalene musculature.

The concept of thoracic outlet syndrome has been embraced hesitantly in many instances because of the protean symptomatic manifestations. The classical shoulder arm pain and paresthesias of the hand are common presenting complaints, but by no means the only ones. In some of these patients headache and neck pain predominate, whereas others complain primarily of chest pain which is often confused with angina pectoris. Still another group has syncope as the primary manifestation with thoracic outlet compression with dizziness and tinnitus that are either accentuated or induced by hyperabduction.

The provocative tests which are not widely known must be applied to patients with shoulder arm syndromes. These include the Adson's maneuver, the costoclavicular maneuver, and hyperabduction. When the thoracic outlet syndrome is present, these tests will commonly precipitate symptoms and/or produce compression of the subclavian artery which can be detected by obliteration of the radial pulse and the production of a bruit in the infraclavicular region. The implication we assume is that the median cord of the brachial plexus which is immediately adjacent to the subclavian artery is also compressed.

It is this neurological ramification that gives rise to the ulnar nerve which carries fibers of C-8 and T-1. There are also three objective tests (namely, nerve conduction velocities, nystagmography and finger plethysmography) which in my experience have added significantly to the diagnosis of this condition. Furthermore, when they are positive, the results of rib resection are likely to be satisfactory. The latter two tests are performed when the patient is carrying out the provocative maneuvers. The casual observer is commonly impressed with those features of personality which tend to label these patients as neurotics with a multitude of psychosomatic complaints. The fact is that most patients have been to several physicians without obtaining adequate pain relief. They look well, but function poorly and are frequently suspected to be malingerers. Although their stories are often difficult to unravel, the objective studies have helped significantly.

Regarding the technique of a first rib resection, we have found that suction drainage is useful to reduce the likelihood of postoperative adhesions which may result in reappearance of symptoms. In many instances we also recommend transection of the posterior as well as the median and anterior scalene muscles in patients whose primary complaints are headache and neck pain.

DR. W. ANDREW DALE (Closing discussion): Dr. Lord and I have discussed these problems many times. I was surprised, when I carefully evaluated these patients by a retrospective study, that many whom I thought had excellent results, and had so classified them in my own mind, actually didn't when I looked at my own followup notes. So it has made me more objective and I now realize that all don't really obtain A-1 excellent results.

In answer to the comment about the embolization from subclavian pressure, the paper to which you refer dealt with 36 patients who had ischemic problems in the hand due to a variety of causes (Dale, W. A., Lewis, M. R.: *Management of Ischemia of the Hand and Fingers, Surgery*, 67:62, 1970.). There were 11 patients with arterial embolism as well as the one mentioned here.

Dr. Timmis, I am in general agreement with you. It is important to emphasize the variability of symptoms. I agree that many of these patients are "kooky", if that's the word you used. The delayed approach and general conservatism is directed toward avoiding operation upon patients who have primarily psychosomatic problems, yet the pain and discomfort of thoracic outlet syndrome often mimicks this since physical signs are often absent.

I agree that the technique should be radical, in the sense that it's important that all of the rib be removed.

Y-U Advancement Pyloroplasty

JUDSON G. RANDOLPH, M.D.

Heineke in 1886 and von Mikulicz in 1887 independently described the popular method of pyloroplasty by longitudinal incision and transverse closure. In some patients, particularly children, the Heineke-Mikulicz procedure has not always been satisfactory because of inadequate size and distortion of the muscular gastroduodenal funnel. In 1958, Moschel and co-workers reintroduced the concept of the Y-V advancement principle to enlarge the pylorus. This operation has not been widely adopted but has a number of attractive features, including simplicity, safety, and maximal channel size with minimal operating time.

The standard Y-V principle has been modified in favor of a broadly based U-shaped pedicle constructed from the presenting surface of the gastric antrum which is advanced into an incision made in the anterior duodenum. This operation has been used in 33 patients, who range in age from 3 weeks to 17 years. They have been variously followed from 6 months to 10 years. The surgical need for pyloroplasty in this group of patients included hiatal hernia with delayed gastric emptying (19 patients); vagotomy for ulcer (7 patients); esophageal substitution (4 patients); vagotomy for reflux esophagitis (2 patients); and, in one instance, revision of an obstructed Heineke-Mikulicz pyloroplasty. Complications have been minimal; gastric drainage has been highly satisfactory. In long-term followup, no ill effect has been seen from the presence of antral mucosa in the proximal duodenum.

THIRTY/THREE INFANTS and children have undergone pyloroplasty at the Children's Hospital in the past 10 years. The major conditions requiring pyloroplasty were 1) delayed gastric emptying associated with hiatal hernia and gastroesophageal reflux, 2) duodenal ulcer, and 3) esophageal replacement for caustic ingestion. The technique used for widening the pylorus in this group of patients is a Y-U plasty; in this procedure a tongue of antrum is advanced into an incision in the presenting surface of the proximal duodenum. The patients have been followed from 6 months to 10 years and the information gained from them forms the basis of this report.

From the Department of Surgery, George Washington University and the Surgical Service of the Children's Hospital National Medical Center, Washington, D.C.

Historical Perspective

In 1919 Dr. Shelton Horsley, in the opening of his paper describing a new approach to pyloroplasty, stated that "there is no excuse for a new operation if the old ones are satisfactory."⁷ Reports dealing with plastic surgery of the pylorus have been many and varied and their proliferation would seem to lend credence to Dr. Horsley's statement that, even today, a perfect pyloroplasty does not exist. In 1886, Heinecke⁵ and a year later Mikulicz¹⁴ separately described experience with a longitudinal incision through the pylorus and the transverse closure which has been used the world over. In 1892, Jabouley⁹ devised gastroduodenostomy for bypassing an obstructed pylorus. Finney,³ of Baltimore, extended the Jabouley incisions, connecting them through the pylorus to achieve a much wider stoma. Horsley (1919),⁷ Judd (1922)¹² and Weinberg (1956)²³ all introduced modifications of the Heinecke-Mikulicz principle, retaining its basic simplicity.

In his beautiful essay on "The Story of Pyloric Stenosis," Ravitch¹⁹ has pointed out that Nicoll of Glasgow in 1906¹⁶ was the first to record surgical use of the Y-V principle at the pylorus. Nicoll performed his operation using a seromuscular incision without entering the mucosa, reporting satisfactory results in several infants with pyloric stenosis. Rosoff,²⁰ has unearthed the fact that Dr. J. B. Blake of Boston described the use of a Y-V pyloroplasty for duodenal ulcer, citing Blake's remarks which were made in discussion of Dr. Horsley's paper of 1919.² Blake should be credited with the observation that this particular pyloroplasty has application to patients in whom an anterior duodenal ulcer must be excised. His description is as follows: "... a procedure

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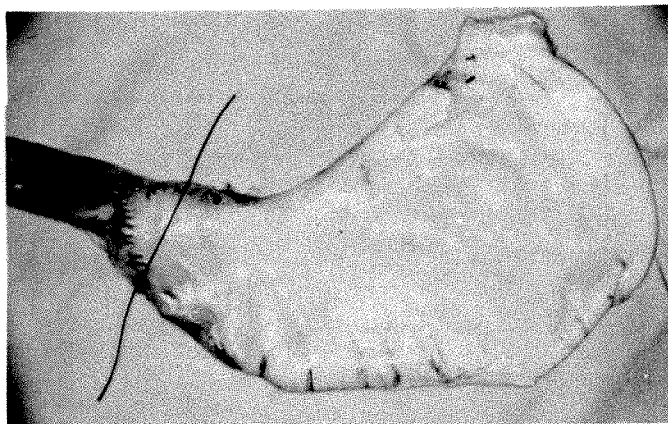


FIG. 1. Formalin specimen of animal stomach after Y-U advancement pyloroplasty. Widening at pylorus is apparent.

which I have employed a number of times after excision of a duodenal ulcer. By taking a tongue-shaped portion of the pyloric antrum and pulling it through the incised ring the defect left by removal of the ulcer may be corrected."²

In 1958 Moschel, Walske and Newmayer¹⁵ described their experience with a pyloroplasty using the Y-V principle. These workers emphasized the need for a blunt or U-shaped pedicle to insure adequate blood supply at the tip of the antral flap. The elegant simplicity of this procedure makes it especially adaptable to young patients where 1) maximal channel circumference, 2) minimal dissection, 3) short operative time, and 4) the least disruption of anatomy are the goals of the operation.

The Y to V plastic operation has been frequently used in pediatric surgery for the correction of various forms of congenital stenosis. Adaptation of this principle seemed a natural step in the treatment of infants and children requiring pyloroplasty.

Laboratory Experience

After the report of Moschel, *et al.*¹⁵ describing satisfactory clinical trials with a Y-V pyloroplasty, the operation was studied in our laboratory to evaluate its immediate and long-term effects in adult dogs and puppies. This experience has been previously reported^{17,18} and is briefly summarized here.

For initial trials a standard Y-V plasty operation was used. Six adult dogs were operated upon and a V-shaped pedicle of the anterior distal antrum was outlined. A longitudinal incision was made in the presenting surface of the duodenum from the pylorus distalward. The pedicle so fashioned was then drawn down into the duodenum and sutured in place. Of the first 6 animals undergoing such an operation, 3 had complications referable to blood supply in the apex of the pedicle. Consequently, the tip of the pedicle was blunted (as Moschel

and co-workers had recommended) and a flap of gastric tissue was constructed so that the tip and the base were of nearly equal width. The tongue of antrum was advanced and sutured into an incision in the anterior duodenum wedging open the pyloric canal (Fig. 1). Twenty such operations were carried out on adult mongrel dogs. The procedure was then performed on 14 recently weaned puppies. Because of other protocol objectives, 10 of the 14 puppies also had a transabdominal truncal vagotomy at the time of pyloroplasty. Weekly weight changes and growth patterns were determined in the puppies. The animals were sacrificed periodically from 4 to 12 weeks after operation.

In the 20 adult dogs undergoing pyloroplasty using the broad-tipped pedicle, there was one leak which the animal survived. At intentional sacrifice, it could not be proved whether this single instance of leakage was attributable to defective blood supply and necrosis or to a technical error at the suture line. Two of the puppies having transabdominal truncal vagotomy and pedicle pyloroplasty died of pulmonary complications at 6 and 21 hours postoperatively. In both, the pedicle appeared healthy, suture lines were intact, and there was no evidence of aspiration. It was concluded that these deaths were associated with the fragility of the young animals and not related to the pyloroplasty. In the other 12 puppies the pyloric operation was well healed at sacrifice (Table 1).

In all of the animals the pylorus was widened by at least 30% of its total circumference. Gastric emptying was seen to be adequate as evidenced by the ability of the dogs to eat a normal diet at regular intervals without vomiting, and by a barium swallow study of randomly selected animals.

Autopsy of all adult and young dogs revealed a well healed gastric pedicle. There was a clean, well healed mucosal junction with no significant tissue turn-in. Of particular interest was the evidence of adaptation of the gastric pedicle to its new duodenal environment. The gastric pedicle became smoothly incorporated into the duodenal wall, (Fig. 2) losing some of its thickness and assuming a texture more nearly that of the thinner duodenum. The dog's pylorus is freely mobile which reduces its comparability to the human subject, but the results of these studies seemed to support the safety and good function of the operation. Accordingly, clinical use was begun in our hospital for those infants and children needing pyloroplasty.

TABLE 1. Y-U Advancement Pyloroplasty in Animals

Type	Number	Deaths	Non-fatal Leaks	Complication Rate
Y-V	6	2	1	50%
Y-U	34	0	1	3%

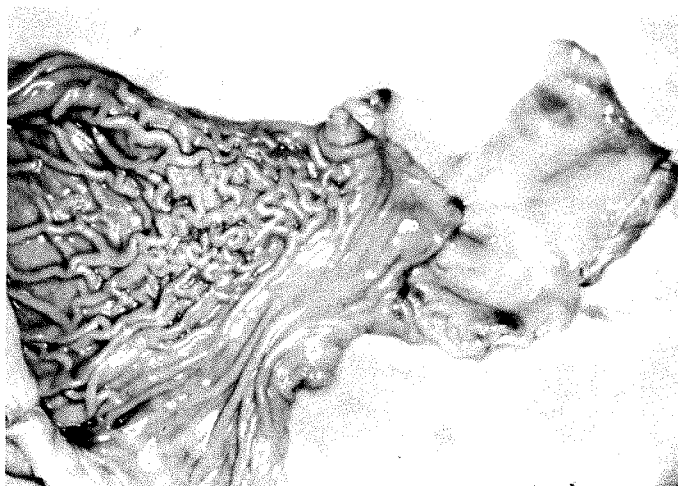


FIG. 2. Formalin-fixed animal stomach opened from posterior aspect to demonstrate healed mucosal surface at site of the pyloroplasty. (Reprinted from *Current Topics in Surgical Research*, 1:291, 1969.)

Operative Technique

A full-thickness, U-shaped pedicle is constructed from nearly all of the presenting surface of the antral portion of the stomach (Fig. 3). The width of the flap should measure at least two-thirds of its length. It is important that the tip be nearly as broad as the base. An incision in the presenting anterior surface of the duodenum is made from the pylorus distalward; this incision should be slightly shorter than the length of the pedicle. To prevent infolding tissue and to assure accurate apposition of the mucosal edges, three sutures in the apex of the antral flap are placed in the manner described by Gambee.⁴ These key sutures are initiated by passing the needle through the full-thickness of the pedicle from serosa to mucosal surface. The needle is then passed out through the antral mucosa only. The stitch is completed by returning the needle into the lumen through the duodenal mucosa, and finally passing it out through the full thickness of the duodenal wall (Fig. 3). When the suture is tied, the mucosal and serosal surfaces of the pedicle are juxtaposed to their counterparts in the duodenum. Three such sutures are placed in the apex of the advanced antrum, securing it to the distal extent of the duodenal incision. The remainder of the closure is carried out with a single layer of interrupted full-thickness silk sutures. (Fig. 4)

Clinical Experience

Pedicle pyloroplasty has been employed in 33 infants and children. Thirteen of the patients were less than 6 months of age at the time of surgery. The indications for operation are shown in Table 2. Two patients had scar and inflammation in the anterior duodenum. A third had an anterior ulcer which had previously perforated but sealed against the gall bladder. The pedicle is an ideal

TABLE 2 *Clinical Experience with Y-U Advancement Pyloroplasty*

Hiatal Hernia or Gastroesophageal Reflux	21
A. Concomitant (for gastric stasis)	15
B. Delayed (for persistent stasis)	4
C. With vagotomy for severe esophagitis	2
Peptic Ulcer	
With vagotomy	7
Esophageal Substitution	4
Revision of Obstructed Heineke-Mikulicz	1
Total	33

way to combine pyloroplasty with excision of the diseased anterior duodenum (Fig. 5). Excision of scar or ulcer and replacement with healthy antral tissue has offered a solid, pliable channel with no difficulty in healing at the duodenal margin. Of special note is an infant who

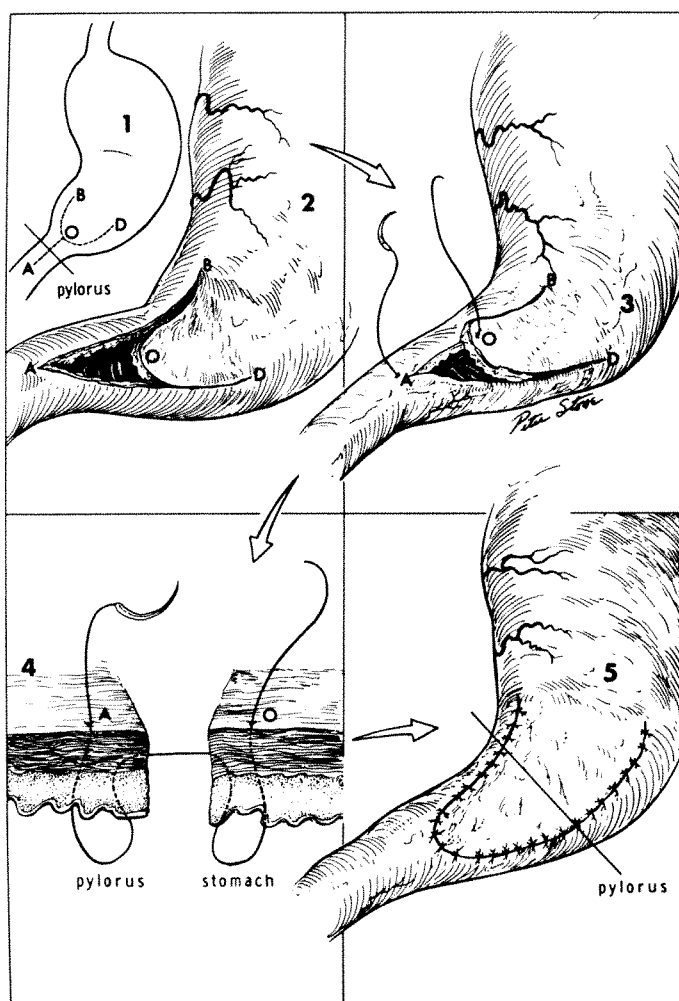


FIG. 3 Diagram depicting steps in the construction of Y-U advancement pyloroplasty. (1) Dotted lines indicate proposed incisions. (2) Line drawing showing completed incision of pedicle and incision in anterior duodenum. (3) Key suture to position antral pedicle in duodenal incision. (4) Diagram depicting Gambee Suture to insure mucosal apposition. (5) Completed pyloroplasty. Line indicates pylorus and demonstrates widening effect of the pedicle advanced.

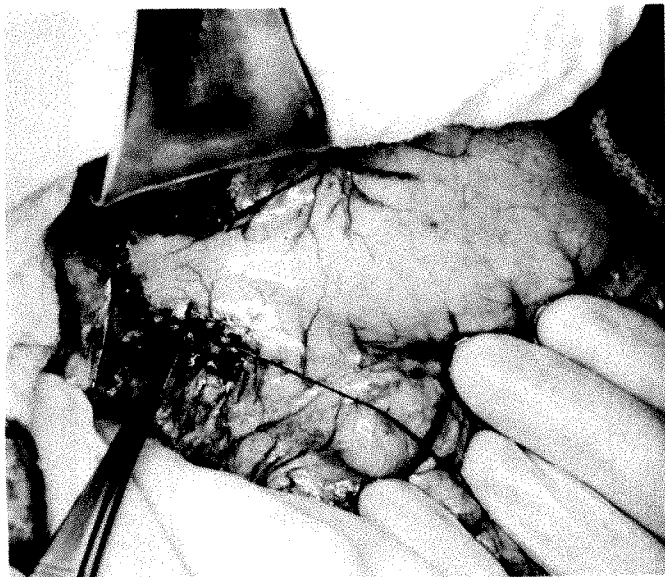


FIG. 4. Operative photograph of completed Y-U pyloroplasty in an infant. (Reprinted from J. Ped. Surg., 6:390, 1971)

had undergone Heinecke-Mikulicz pyloroplasty but was completely obstructed at the site of the previous operation. Conversion of this mechanical problem by using the Y-U operation was ideal and obviated the need for gastrojejunostomy (Fig. 6).

Pyloroplasty by advancement of the antral pedicle has proven to be structurally sound in pediatric patients. Operative time is short and there have been no significant postoperative complications. In all patients, gastric emptying has been prompt, as determined by postoperative barium studies. None of the patients have had subsequent clinical problems related to the pylorus, and there have been no late problems with respect to growth

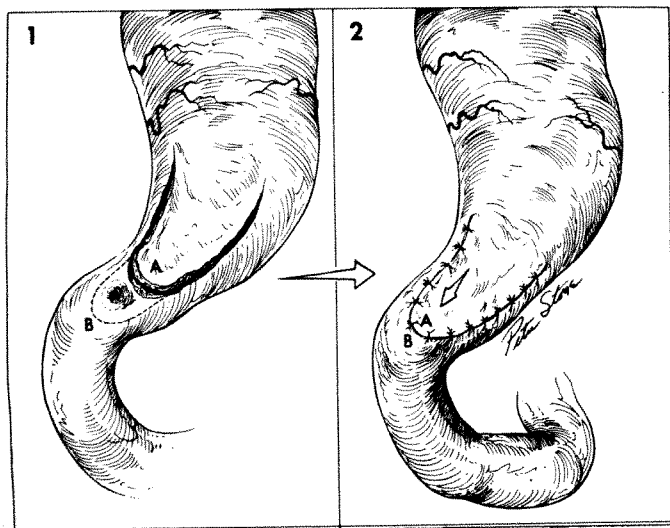


FIG. 5. Diagram showing excision of duodenal ulcer and replacement by antral pedicle.

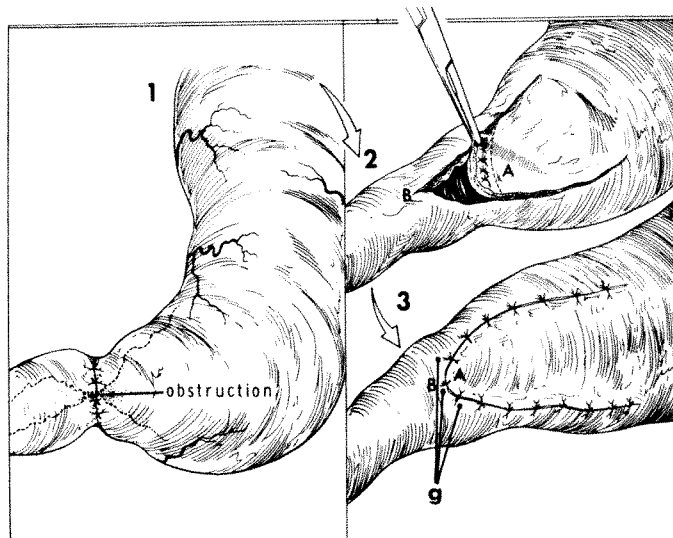


FIG. 6. Diagram showing use of antral pedicle to widen pylorus obstructed at site of previous Heinecke-Mikulicz operation.

of the stomach or pyloric canal in long term followup of these growing subjects.

Discussion

The studies of Sawyers and Scott,²¹ and Wise and Ballinger²⁴ underscore the fact the pyloroplasty will continue to be a useful component in the surgical treatment of peptic ulcer. This is especially true for children where pyloroplasty with vagotomy is recommended as the operation for the younger subjects^{10,22} because it produces the least anatomic derangement and the least disturbance of physiology. Pyloroplasty has also been used in infants as a complementary procedure in repair of hiatal hernia and gastroesophageal reflux.^{11,13} Some children with caustic strictures of the esophagus have had such extensive inflammation that vagal function has been impaired; for these patients pyloroplasty has been necessary to improve gastric emptying.

As in the adult, effective gastric emptying *via* an adequate lumen is the prime consideration of pyloroplasty in infants and children. There are additional unique demands of pyloroplasty in young patients. For example, it is highly desirable that the pylorus be open and functioning early in the postoperative course of the neonate. Operative time is another significant factor in the thermolabile infant, and thus the operative procedure must be simple in design. In small patients, the Heinecke-Mikulicz pyloroplasty sometimes fails to provide adequate gastric drainage because the internal diameter of the passage thus created may be no larger than the infant's uncorrected pylorus.

In an article supporting the Jabouley procedure, Hurwit and co-workers⁸ have cited some of the disadvantages of the pyloroplasty of Heinecke and Mikulicz. Ac-

cording to these authors, the difficulty of performing the operation in an inflamed, scarred duodenum and the possibility of narrowing the pylorus by reduction of the AP diameter are serious detractors. Additionally, Ballinger and Solanki¹ have emphasized that the Heinecke-Mikulicz procedure suffers from distortion of the normal antral funnel and disruption of antral peristalsis. Those surgeons who have been concerned about the inadequacies of the Heinecke-Mikulicz procedure have generally resorted to the Jabouley or the Finney drainage procedures.⁶ The advantage of the excellent opening provided by the Finney pyloroplasty or the Jabouley gastroduodenostomy is offset in infants by the more extensive dissection and increased operative time required for its construction. Ballinger's suggestion¹ of widening the pylorus by a jejunal patch has certain mechanical advantages to recommend it. However, the same objective can be achieved by advancing the gastric pedicle which, in turn, creates a more anatomic funnel. This latter benefit has particular merit in young patients.

The theoretical objection of transposing gastric antrum into contact with the alkaline duodenal content, thereby stimulating gastric secretion, has not proven clinically significant. It is likely that most successful pyloroplasty procedures create a mixing chamber of gastric and duodenal content in the region of the pylorus.

This Y-U operation produces a wide pyloric channel without extensive dissection or prolonged operative time and these salutary features are particularly appealing in infants and children. Preservation of a neuromuscular funnel at the pylorus is suggested by fluoroscopic study of these patients. Its use in a patient who was obstructed after a Heinecke-Mikulicz pyloroplasty is another successful application of the procedure. An added dividend of the Y-U pyloroplasty, which may have special pertinence for adults, is its adaptability to patients with an acute ulcer or scar in the anterior duodenum.

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DISCUSSION

DR. GEORGE A. HIGGINS, JR. (Washington, D. C.): About two years ago one of the residents who had rotated through Dr. Randolph's service came onto our service and began talking about this "cool" method of doing a pyloroplasty.

We were working on patients at opposite ends of the chronologic

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spectrum; but I went through my files and dug out a slide showing this technique which we had learned from Ben Walske, who was the co-author of the Moschel paper in 1958. We have used this on a number of occasions for pyloroplasty, and have found it to be quite satisfactory. So I can also commend it to you as another tool in your surgical armamentarium.

Hepatic Portoenterostomy:

An Assessment of Its Value in the Treatment of Biliary Atresia

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A series of 12 infants undergoing hepatic portoenterostomy for incorrectable-type biliary atresia is reviewed. There has been no evidence of a sustained postoperative increase in bile excretion or improvement in biliary cirrhosis in any patient. Survival statistics for the group as a whole are poor with a mean postop survival time of 11 months and a mean total survival time of 15.3 months. These survival times are worse than that previously reported for infants with untreated biliary atresia. Our disappointing results with hepatic portoenterostomy raise doubts concerning its value in the treatment of biliary atresia.

ADEQUATE surgical drainage of the biliary tree in infants with biliary atresia remains an unsolved problem for the majority of such infants have an incorrectable type lesion, *i.e.*, no extrahepatic bile duct is available for anastomosis to the intestine. The history of attempts to surgically circumvent this problem has been most depressing. Claims of success with such procedures as the use of artificial bile ducts,¹⁰ the drainage of thoracic duct lymph,^{1,11} and hepatic lymphatic drainage to the G.I. tract⁴ have all eventually proven to be false.

Biliary atresia, for some unexplained reason, appears to be more common in Japan than elsewhere. Interest in ameliorization of the disease by surgical means has therefore flourished in that country. In 1957 Kasai⁸ first reported the use of hepatic portoenterostomy as a means of dealing with incorrectable types of biliary atresia, and subsequently claimed a cure rate of approximately 10%.⁷ A more recent report, combining several large Japanese series,² claims an approximately 40% cure rate for infants

with biliary atresia using Kasai's basic technique together with sundry modifications.

The optimism engendered by the reports of Kasai and others in Japan led us 5 years ago to begin performing hepatic portojejunosomies on all infants with biliary atresia in whom an extrahepatic bile duct was not available for anastomosis to the intestinal tract. The diagnosis of an incorrectable-type lesion was made at surgery after operative cholangiograms and careful dissection of the porta hepatis. All infants undergoing hepatic portoenterostomy have been under continual close postoperative surveillance.

Clinical Material

Between June 1969 and December 1974, we have seen 12 infants with incorrectable-type biliary atresia at Oklahoma Children's Memorial Hospital. Prior to surgical exploration, all underwent extensive evaluation to rule out other possible causes of persistent neonatal jaundice. The evaluation of persistent neonatal jaundice at our institution includes serum Lipoprotein-X determinations before and after a short course of cholestyramine.³ The first 10 patients in our series were also evaluated with double¹³¹ I-Rose Bengal excretion tests as reported by Poley, *et al.*⁹ Percutaneous needle biopsy of the liver was a routine part of the diagnostic work up in all patients studied.

All infants were explored as soon as possible after making the diagnosis of biliary atresia. Exploration was done through a long, right subcostal incision which ex-

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tends across both rectus muscles. The peritoneal cavity is explored and wedge biopsies of the liver obtained. We then proceed exactly as outlined by Kasai in his original reports.⁷ We have deemed it inadvisable to use any of the technical modifications which were reported by Kasai and his co-workers⁶ after the onset of our study. Attempts are first made to locate the extrahepatic biliary tree or a portion thereof through which to perform a cholangiogram. If an extrahepatic bile duct or gallbladder is identified, it is cannulated with a fine polyethylene catheter and flushed with sterile saline. An operative cholangiogram is then performed by the gentle injection of 4 to 5 cc of 50% Hypaque through the catheter. If an extrahepatic biliary tree or portion thereof is not identified with the above maneuvers, the gallbladder and cystic duct are dissected free and dissection of the porta hepatis carried out. If an extrahepatic biliary tree is still not identified, a transverse incision is made on the anterior surface of the hepatoduodenal ligament and the mass of tissue lying anterior to the hepatic artery and portal vein dissected up to the hilum of the liver. This mass of prevascular tissue is dissected as close as possible to the liver substance and the specimen removed for microscopic examination. A Roux-en-y type portoenterostomy is carried out between the small remnant of connective tissue left at the liver hilum and the proximal jejunum. The Roux-en-y anastomosis is constructed so as to form a 25 to 30 cm jejunal spur. This segment of jejunum is brought up to the stump of the tissue dissected off the vessels of the porta hepatis through the transverse mesocolon. The area of anastomosis is drained through a separate lateral stab wound.

All infants undergoing hepatic portoenterostomy have received close continuous postoperative surveillance. All survivors are readmitted every 3 months and evaluated with liver function studies and percutaneous needle biopsy of the liver. For the past two years, we have also included serum Lipoprotein-X determinations and¹³¹I-Rose Bengal excretion studies as a routine part of this evaluation.

Autopsies were carried out in 4 of the 9 deaths. A needle biopsy of the liver had been performed within 3 months of death in all infants in whom an autopsy was not performed.

Results

We have had one postoperative death in our series of 12 patients for an operative mortality of 8.3% (Table 1). This death was due to respiratory complications which developed on the day of surgery. The patient (L.W.) was 13 months of age and in end-stage liver failure at the time of surgery.

There have been three significant postoperative complications for a complication rate of 25% (Table 2). Patient K.W. (Table 1) developed massive upper gastroin-

TABLE 1. *Survival Statistics in Infants Undergoing Hepatic Portoenterostomy*

Patient	Age at Operation (Mo.)	Postop Survival Time (Mo.)	Total Survival Time (Mo.)
JW	5	52*	57*
LW	13	0	13
JF	3	2	5
JV	3	10	13
GM	3	10	13
KW	2.5	3.5	6
DG	2.5	11	13.5
AS	2	15	17
MH	8	4.5	12.5
AF	2.5	14**	16.5**
CB	4	3.5	7.5
BB	2.5	7**	9.5**
MEAN	4.3	11.0	15.3

*Orthotopic liver transplant at 52 mos post hepatic portoenterostomy

**Alive, terminal liver failure

testinal bleeding secondary to multiple gastric stress ulcers in the first week postop. She required vagotomy and pyloroplasty for control of the hemorrhage. Patient B.B. required exploratory laparotomy 8 days postop for intestinal obstruction secondary to adhesions. At the time of exploration, a right subphrenic abscess was discovered and drained. Patient M.H. suffered from moderately severe upper G.I. bleeding in the first week postop. He required blood transfusions, but the bleeding ceased spontaneously without surgical intervention. Upper G.I. series failed to reveal the source of the bleeding.

Liver biopsies taken at the time of operation have shown evidence of biliary cirrhosis in all patients, despite the fact that the majority were under 3 months of age. The degree of cirrhosis has correlated roughly with the age at operation. Infants operated on at 3 months of age or younger have shown primarily severe cholestasis and early fibrosis while several of the older patients have had full blown biliary cirrhosis at the time of surgery. Subsequent evaluation of hepatic morphology by both 3 monthly needle biopsy and autopsy examination has revealed a steady progression of the cirrhosis in all 12 infants. The microscopic findings have been those of increasing fibrosis, cholestasis and hepatocyte loss.

TABLE 2. *Postop Complications in Infants Undergoing Hepatic Portoenterostomy*

	2
Upper G.I. Bleeding Requiring Transfusion	12 = 16.7%
	1
Intestinal Obstruction Secondary to Adhesions	12 = 8.3%
Total Post Op Complication Rate	= 25 %

Survival data is outlined in Table 1. The average age at operation was 4.3 months. This is skewed by patient L.W. who was 13 months of age at the time of hepatic portoenterostomy. The mean postoperative survival time is 11 months. Patient J.W., the first patient in our series, underwent an orthotopic liver transplant 52 months post hepatic portoenterostomy for end-stage liver failure. Her postoperative survival time has been calculated to the time of liver transplant.

The mean total survival time for the 12 patients is 15.3 months (Table 1). Three patients are still alive. Patient J.W., who underwent a liver transplant, is still alive and doing well 14 months post transplant. Her total survival time has been calculated to the time of transplant. Two other patients, A.F. and B.B. are still alive 14 and 7 months post hepatic portoenterostomy. Both patients are in end-stage liver failure with markedly abnormal liver function studies and liver biopsies showing evidence of

rapidly progressing biliary cirrhosis. Both suffer from severe ascites which is difficult to control with diuretic therapy. Both are now considered candidates for liver transplant.

Comprehensive evaluation of our postoperative survivors, which is carried out every 3 months, has been remarkably similar in all patients. Although serum bilirubin levels will sometimes show intermittent improvement, we have not seen continued improved bile excretion or a return of bilirubin levels to normal in any patient. Hepatic excretory function as measured by LP-X determinations and ^{131} I-Rose Bengal excretion studies has been evaluated in our last 5 patients. We have been unable to demonstrate any improvement in hepatic excretory function by such means in any of the 5 patients.

The terminal course of all 9 patients who have expired has been tragically similar, i.e., upper G.I. bleeding, liver failure and sepsis.

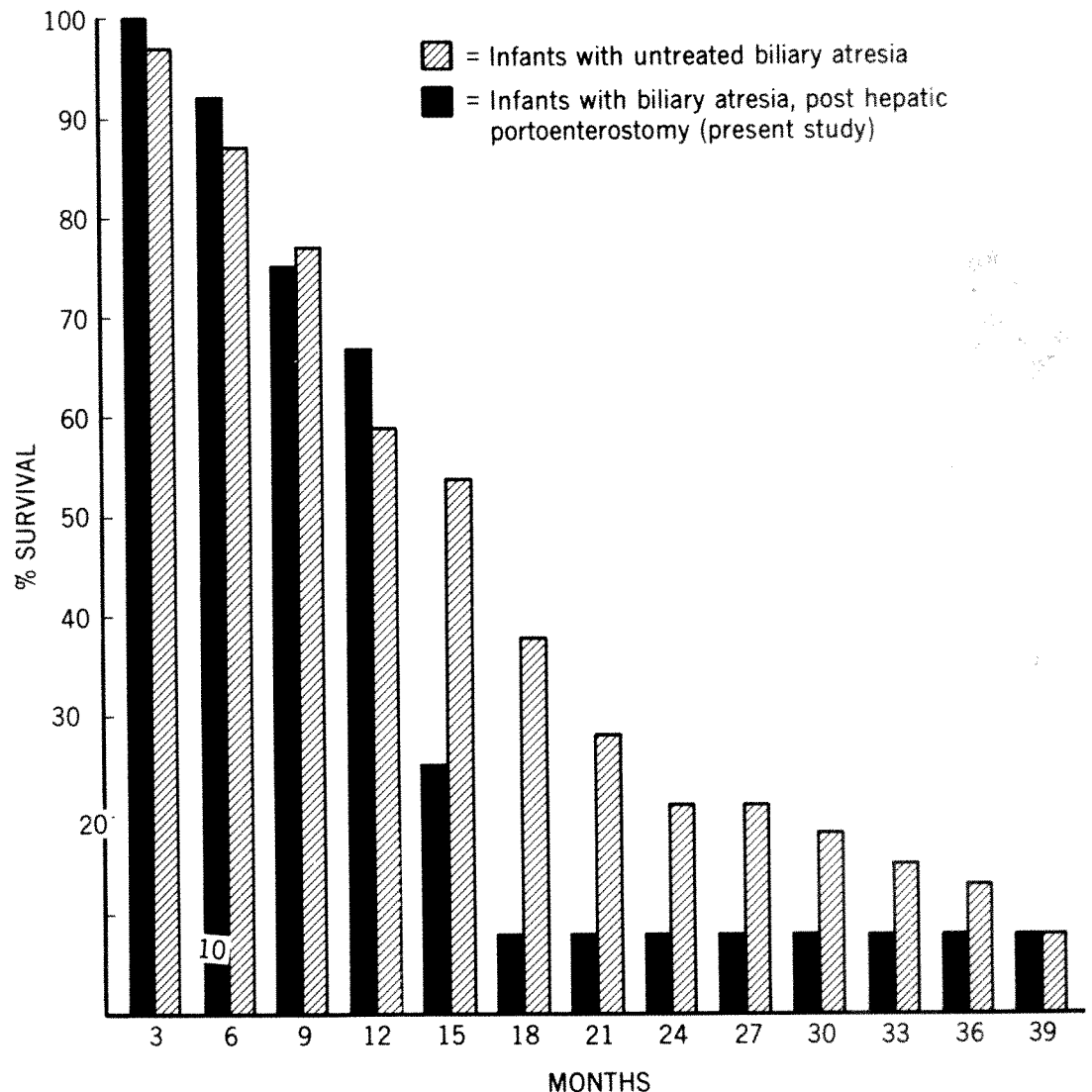


FIG. 1—Survival comparison in infants with untreated biliary atresia and those with biliary atresia posthepatic portoenterostomy.

Discussion

Bill² has recently reviewed a combined series of infants in Japan undergoing hepatic portoenterostomy for incorrectable biliary atresia between 1968 and 1971. This combined series shows a 43% cure rate for infants undergoing hepatic portoenterostomy before 3 months of age, and 7% cure rate for infants operated on after 3 months of age. Eight or 67% of the infants in our series were 3 months of age or younger at the time of surgery. We have seen no cures with hepatic portoenterostomy. In fact, the mean postop survival time is only 11 months despite patient J.W., who lived for 52 months before liver transplant. The mean total survival time is only 15.3 months, which is actually less than the average total survival time reported previously by Hays and Snyder⁵ for infants with untreated biliary atresia. Hays and Snyder had two patients who survived longer than 53 months without treatment, so one must be wary of supposed cures reported as early as one year postop. If one plots the survival statistic for our series of 12 infants who have undergone hepatic portoenterostomy, against the series of untreated infants reported by Hays and Snyder (Figure 1), one notes that there is no significant improvement in survival with hepatic portoenterostomy. One must conclude that hepatic portoenterostomy provides no therapeutic advantage in the treatment of biliary atresia.

Since the Japanese combined series² totals 215 patients, one can question whether our series is large enough to be significant. Statistical evaluation of our data shows that if the expected cure rate for the procedure is 10%, the probability of our having no cures in 12 patients solely by chance is 28.2%. If the expected cure rate is approximately 40%, as reported in the latest Japanese series, the probability of seeing no cures in 12 patients drops to 0.21%. One must conclude that the probability of our having no cures, purely by chance, is quite remote.

One may logically ask if we are continuing to perform hepatic portoenterostomies on infants with incorrectable

types of biliary atresia. We are continuing to perform the procedure for, at present, we have nothing other than liver transplant to offer these unfortunate infants. Transplant surgeons, in general, do not believe that a previous hepatic portoenterostomy interferes with the performance of a liver transplant. They, in fact, use the Roux-en-Y limb of jejunum to drain the biliary tree of the transplanted liver. This is considered an advantage for it means one less anastomosis to perform at the time of transplant and also one less anastomosis to cause problems in the post transplant period. In addition, statistical evaluation reveals that if one accepts the 10% cure rate originally reported by Kasai,⁷ there is a 28.2% probability that we have seen no cures with hepatic portoenterostomy because our series is not yet large enough.

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DISCUSSION

DR. LOUIS D. SHAFFNER (Winston-Salem, North Carolina): The pessimism expressed by the authors here, Dr. Williams, forces me to say that I do not think we should take this with such pessimism. There is nothing better at the present time that we know to do.

When we operate on these babies, we want to know if they have neonatal hepatitis or biliary atresia. If an operative cholangiogram shows no patent biliary ducts, we assume there is a biliary atresia. We then explore the porto hepatic, looking for a duct which we can anastomose to the bowel.

Once we have explored the porta hepatis and find no macroscopic ducts, we leave a raw area with residual strings of nondescript tissue. It has been our experience, and reported by others, that an exploration without an anastomosis shortens the life of the baby. It shortens it by not only the effect of the anesthesia but also by an increase in ascites with its attendant protein loss, distention, et cetera.

If we can do a portoenterostomy, and if there are patent ducts there, maybe some bile will come through.

We have had experience with only three patients. Two are still alive, one for 18 months and one for four months. The first initially had a repair of a jejunal atresia and an accompanying gastrostomy. A portocholecystostomy was done one month later with resulting clearing of the jaundice. One year later the liver was biopsied at the time of closure of the gastrostomy. Residual cirrhosis was prominent but the fibrosing process did not appear to be active. The baby has continued to do well. The liver is still palpable. We admit the baby may eventually show liver failure, but we certainly are better off than if we had not tried.

In the last patient we performed the Kasai procedure, a double Roux-en-Y with a jejunostomy stoma. Bile drainage through the stoma has been so persistent that the mother has said, "Please close it, because the bile is running all over the baby's clothes, and I cannot keep her clean." Kasai has recommended that the jejunostomy be made as a safety valve to guard against retrograde cholangitis from any intercurrent gastrointestinal upset. He recommended that this be left open for six months to one year. The baby's liver enzymes have returned to normal and bilirubin from 16 mg% to normal.

In the tissue removed from these two cases microscopic ducts, or at

least epithelial lined tracts, were found, 50 μ in diameter in one and up to 100 μ in diameter in the other. No ducts were found in the baby who put out no bile.

Our results so far are encouraging, and we feel the procedure is worth the effort as the best currently available.

DR. JUDSON G. RANDOLPH (Washington, D.C.): This is a very discouraging problem, and I think the group at Oklahoma is to be congratulated on this frank courageous presentation.

I'd like to present to you data from the work that's going on in our clinical research center under the direction of my colleague, Dr. Peter Altman. We have studied 16 patients with biliary atresia in the last 22 months. One of the differences in our experience from that reported by Dr. Williams and Dr. Campbell and their co-workers may be based on our decision not to operate on any children that are over three months of age.

(Slide) The dissection must be carried well into the hilum. A frozen section of the tissue to be used for anastomosis is essential to assure the presence of duct structures. We chip away at the liver until we find a series of tiny ducts, then the stomal loop is put around this area, as Kasai had described.

(Slide) Here's one of our patients whose preoperative liver scan had no isotope coming from the liver. Yet, here in the postoperative period some months later, normal activity flow into the intestine can be seen.

(Slide) This shows one of our patients who is completely free of jaundice. Naturally, I picked one of our best babies to show you.

(Slide) Here are the data from this group of patients. Sixteen patients, in seven of whom there was no drainage. In this group are two patients over three months of age. Here there were nine who had biliary drainage, and these patients have been followed from 6 to 22 months. One died early in the postoperative period. These other eight survivors have liver scans, showing normal amounts of radioactive material excreted, and none of them are clinically jaundiced. Their bilirubin range is between 3 and 1. So, 50% of the patients are draining apparently normal amounts of bile.

But note that five of the eight survivors have continued cirrhosis, as

indicated on their subsequent biopsy studies; some open, some by needle. Only one had no cirrhosis, although two are not yet biopsied, they are so early in their postoperative course.

This would indicate that in spite of biliary drainage by the Kasai procedure, we're still seeing on-going fibrosis, as if there is more to the etiology, or the pathophysiology, of biliary atresia than just absence of ducts. But we are encouraged, and will continue to study and operate on those patients that are under three months of age.

DR. DAVID P. CAMPBELL (Closing discussion): I would like to thank our discussants. I agree with both Dr. Shaffner and Dr. Randolph that these patients are, in general, a very discouraging group. We have, however, not given up the procedure despite our rather disappointing results.

One must be hesitant in claiming satisfactory operative results in these infants prior to two to three years postop, because, as per the last slide shown by Dr. Williams, they may live for four years or more without any treatment. I would also like to emphasize the fact that there may be great fluctuations in liver function studies, including serum bilirubin, in the postoperative period. Statements regarding immediate improvement in liver function postoperatively must therefore be evaluated with caution. A rather prolonged period of postoperative evaluation is necessary, for despite intermittent decreases in serum bilirubin levels and what seems to be evidence of improved hepatic excretion of bilirubin, there is a continual discouraging increase in the fibrotic process within the liver.

I think that Dr. Randolph hit the nail on the head when he said there is much more to the pathophysiology of biliary atresia than obstructed bile ducts. We presently believe, as do other workers in the field, that biliary atresia and neonatal hepatitis are different expressions of the same disease, i.e., an inflammatory process of unknown etiology involving the biliary tree and periductal hepatic tissue. This inflammatory process may clear spontaneously and be labeled neonatal hepatitis or, in a small percentage of patients, progress to fibrosis of the biliary tree and surrounding tissue and present as biliary atresia.

Use of Radionuclide Imaging in the Early Diagnosis and Treatment of Renal Allograft Rejection

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Data are presented on the clinical application of radionuclide imaging to evaluate changes in cadaver transplant function in the immediate postoperative period. The method uses orthoiodohippuric acid (hippuran) administered IV, with scintillation imaging, and curve analysis by a digital computer. An initial study is always obtained 24 hours after transplantation. Serial studies are then obtained, as needed, to interpret the clinical course. Selected cases are presented which illustrate the use of this protocol in various clinical settings. In the oliguric patient serial studies have been of particular value. They have identified ATN so that over-enthusiastic treatment for rejection could be avoided. They have also identified acute rejection complicating ATN so that high dose steroid therapy could be administered appropriately. In the non-oliguric patient they have frequently contributed to the early diagnosis of acute rejection, and they have been useful in monitoring the effect and duration of treatment for severe rejection crisis. It is concluded that radionuclide imaging studies, when carefully applied and interpreted, are a valuable adjunct to the management of patients in this complex clinical setting.

RENAL TRANSPLANTATION of cadaver kidneys has become an increasingly successful operation in the therapy of patients with terminal renal disease.¹ Following the transplantation of the cadaver kidney, there frequently is a period of severe oliguria or anuria which is difficult to evaluate by clinical and biochemical means.¹² This is a major diagnostic dilemma. During this period the transplant is prone to a variety of catastrophic events, including acute tubular necrosis (ATN), early rejection, rejection superimposed on ATN, major vascular occlusion, or ureteral obstruction.¹⁰ The ability to detect and differentiate acute rejection from other causes of oliguria in the transplanted kidney has important therapeutic implications since appropriate aggressive treatment may salvage a kidney which might otherwise be permanently damaged or lost.

A protocol for a safe and non-invasive technique of

radionuclide imaging of all cadaver transplants has been developed at North Carolina Memorial Hospital, similar to that which has been described in the literature.^{2-4,6-8,11,13-16,19,20} This paper will present a description of our technique and its application to patients which permits differentiation of the following four possible clinical courses of the transplant: 1) Uncomplicated transplantation; 2) Oliguria established after the first 24 hours post-transplantation secondary to ATN; 3) Severe acute rejection requiring prolonged aggressive immunosuppressive therapy. 4) Early rejection crisis superimposed on established ATN.

Technique

Fifty microcuries of ¹³¹I orthoiodohippuric acid (OIH) are given intravenously and serial 5 minute polaroid images of the kidney and bladder are obtained using a scintillation camera. Simultaneously, the information from the camera is stored on a digital computer (PDD-11 DEC CORP-MAYNARD MASS). The information stored on the computer is then analyzed to selectively graph the transit of OIH through the cortex and medullary portions of the kidney. The curves of the OIH transit are obtained from a selected area of renal parenchyma excluding the collecting system.

Clinical Protocol

The initial study, at 24 hours post-transplant, will reflect the damages associated with cadaver kidney procurement and preservation. Prompt uptake of OIH indicates a patent arterial and venous vascular system. The

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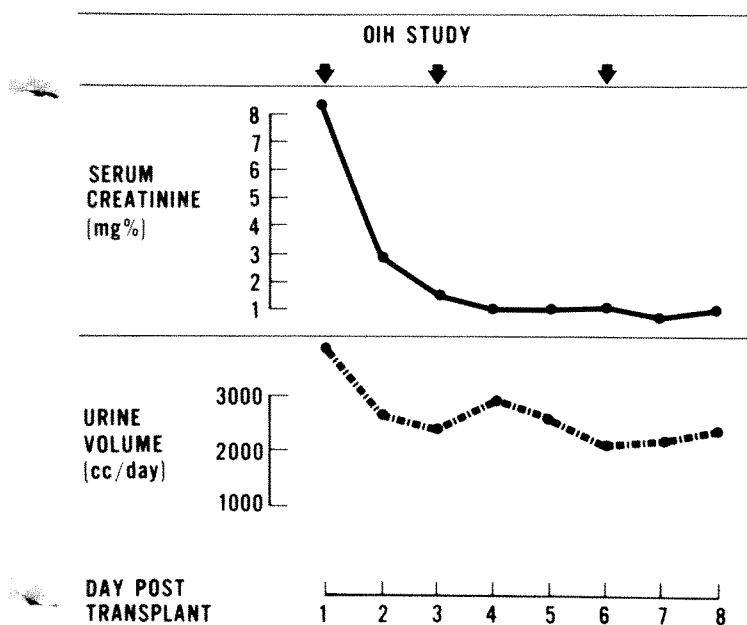


FIG. 1. Clinical course of uncomplicated transplantation.

presence of OIH in the bladder excludes complete obstruction of the collection system. The uptake and excretion of OIH in the cortex and medulla of the transplant on the first postoperative day serves as a baseline for any subsequent "functional impairment." Any deterioration of the transplanted kidney's ability to take up or excrete OIH on serial scans after 24 hours is consid-

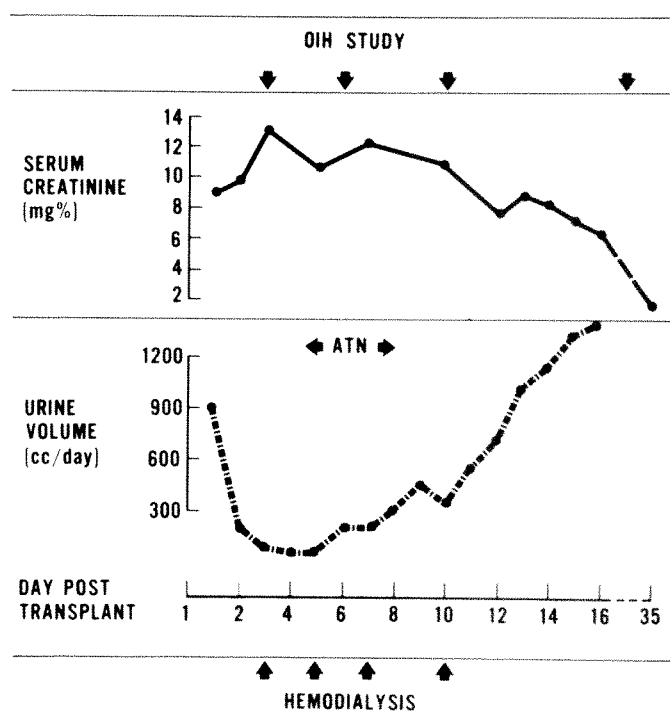


FIG. 3. Clinical course of acute tubular necrosis which resolved.

ered secondary to rejection, obstruction or pre-renal causes. Serial OIH studies are obtained every 2 to 3 days following the transplant until: 1) ATN has resolved and renal function is normal; 2) rejection is successfully treated; or 3) early biopsy dictates the need for removal of the transplant. Any sudden deterioration in the clinical status of the patient after 24 hours constitutes an indication for a repeat OIH study.

Patient D.R.—Uncomplicated Transplant (Figs. 1 and 2). A 22-year-old Caucasian man received a one antigen match cadaver transplant from a donor in an adjacent operating room. Urine output was excellent in the immediate postoperative period and remained good during the next six days as renal function rapidly improved. Serial OIH studies on days one, three and six showed progressive improvement in uptake and excretion of the radionuclide. The abnormality on the initial study was interpreted as consequent to the damage associated with cadaver procurement. The patient left the hospital with normal renal function (creatinine, 1.0 mg%) after two weeks.

Patient A.C.—Severe ATN (Figs. 3 and 4). A 40-year-old Negro woman received a renal transplant removed from a cadaver donor in the adjoining operating room. Despite adequate initial urine output (900 cc's in the first twelve hours), oliguria developed during the next eight days and the patient required hemodialysis four times.

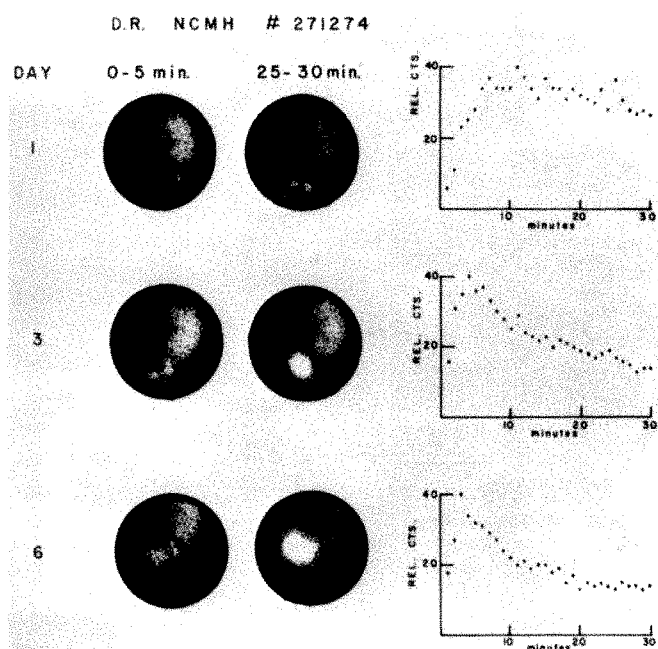


FIG. 2. OIH images and curves obtained on days 1, 3, 6 after transplantation. Mild functional impairment is present on day 1 which becomes normal by day 6.

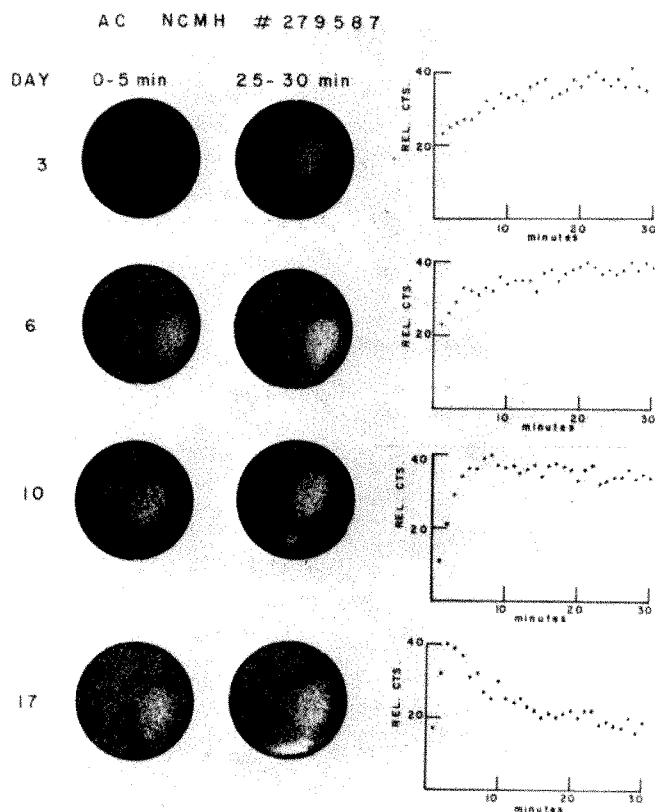


FIG. 4. OIH images and curves in this patient demonstrate marked initial functional impairment with progressive improvement in amount of activity in the kidney, eventual appearance in the bladder (day 10, 25-30 min image) and progressive improvement in the curves.

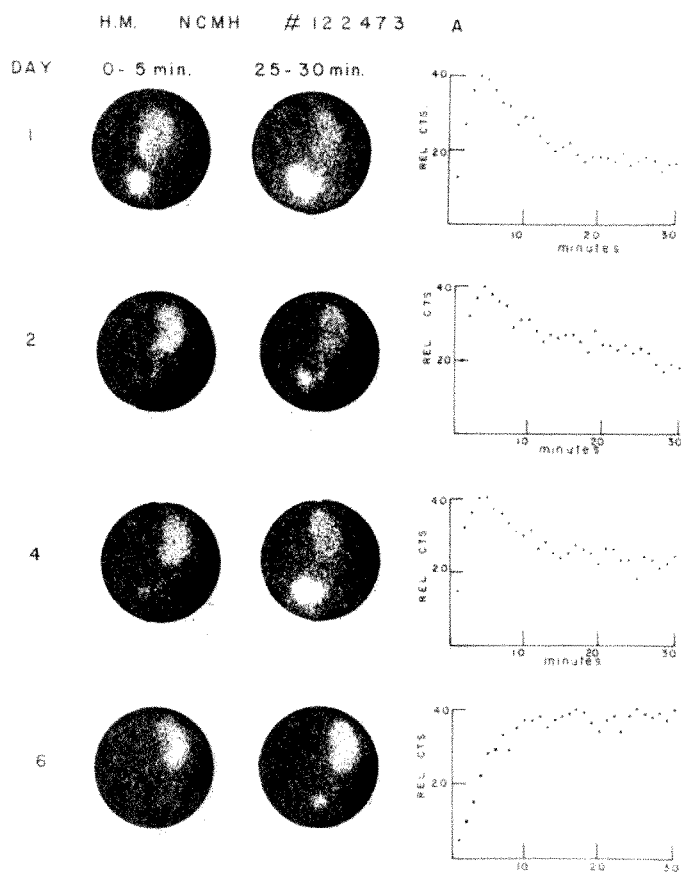


FIG. 6. OIH images and curves in this patient were within normal limits on day one but showed minimal deterioration on day two with less activity in the bladder and a more prolonged clearance ($T_{1/2}$ equal to approximately 25 minutes). Slight improvement in images on day 4 but further marked deterioration on day 6.

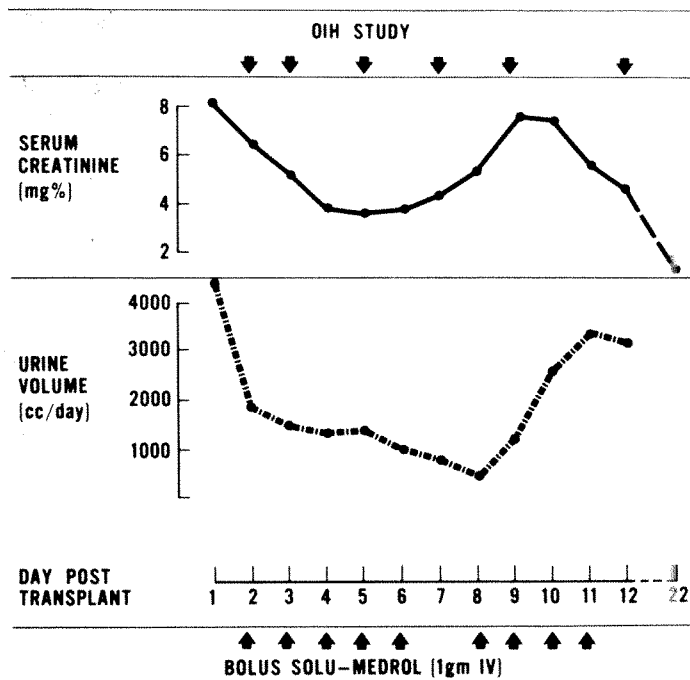


FIG. 5. Clinical course of severe acute rejection requiring prolonged aggressive immunosuppressive therapy.

Thereafter, the clinical course was characterized by a progressive increase in urine output and improvement in renal function. The initial OIH scan on the third post-transplant day revealed delayed and progressive OIH uptake but no excretion. A repeat scan on postoperative day 6 was unchanged from the initial study. However, on postoperative day 10 there was improvement in the uptake of OIH with excretion of the radionuclide within thirty minutes. In this patient, the improvement in OIH uptake and excretion was thought to be indicative of resolving ATN, rather than rejection, which initially would have shown a deterioration in the image. On the basis of the serial OIH studies, immunosuppressive treatment was kept to a minimum during the extended period of oliguria and potentially dangerous levels of immunosuppressive drugs were avoided. The patient was discharged on postoperative day 23 with a creatinine of 2.9 mg%. Ten days later the creatinine was 1.3 mg%.

Patient H. M.—Severe Acute Rejection (Figs. 5, 6 and 7). A 23-year-old Negro man received a two antigen match cadaver kidney. Urine output the first postopera-

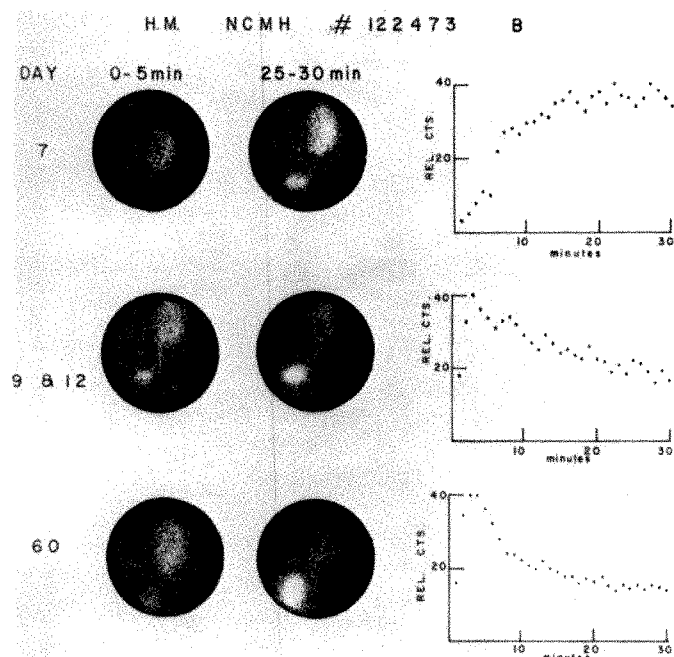


FIG. 7. Day 7 images and curve appear the same as on day 6 (Figure 6). Improvement in the images with early bladder activity and definite change in curve on day 9 and 12. By day 60 the curve and images appear normal. (Figures 5, 6 and 7 should appear together if possible)

tive day was excellent and the baseline OIH scan showed prompt uptake and excretion. Later during the day, urine output diminished acutely, fever and hypertension developed. Therapy for acute rejection was initiated with

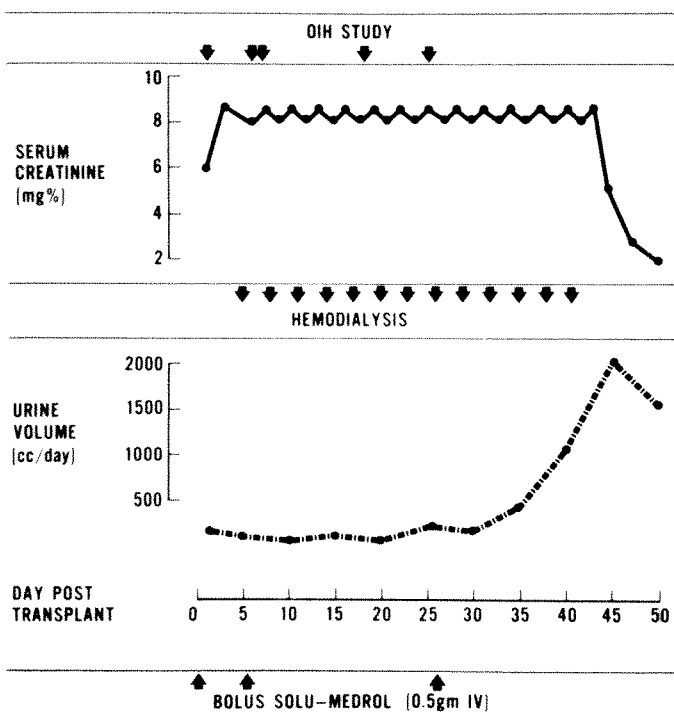


FIG. 8. Clinical course of early rejection crisis superimposed on established acute tubular necrosis.

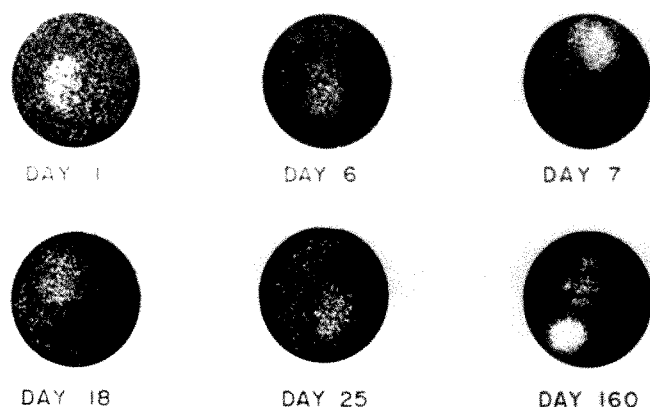


FIG. 9. Single images of the transplant are presented at different post-operative days. Bladder activity was absent on initial studies (days 1, 6, 7, 18, and 25). On day 6 there is less activity in the transplant image than on day 1. Similarly, there is decreased activity in the images obtained on day 18 and 25. A normal image was obtained on day 160.

bolus doses of methylprednisolone. A repeat study on the following day (day two) revealed a slight decrease in OIH excretion consistent with the clinical impression of acute rejection. Following four days of bolus methylprednisolone treatment (1 gram intravenously each day), there was slight improvement in OIH uptake but over the next two days fever again developed and was associated with a decrease in renal function and urine output.

Repeat studies on postoperative days 6 and 7 showed another decrease in OIH uptake and excretion by the transplant. These scans led to 4 more days of treatment for acute rejection. During this period, scans on postoperative days 9 and 12 showed progressive increase in OIH uptake and excretion. Concurrently, the urine output increased and serum creatinine began to return to normal. The patient was discharged on the nineteenth postoperative day with a creatinine of 1.7 mg%.

*Patient D.F.—Acute Rejection Superimposed on ATN** (Figs. 8 and 9). A 22-year-old man received a cadaver kidney which had 295 minutes of ischemia of which 35 were warm. There was a 30 day period of postoperative oliguria. The initial OIH scan on the first postoperative day showed uptake of OIH but no excretion, thus being compatible with the uncomplicated ATN of cadaver procurement and preservation. A repeat scan on the sixth postoperative day revealed a decrease in the uptake of OIH and still no excretion. This was interpreted as rejection superimposed on ATN and therapy with a bolus dose of steroid was given. The OIH scan the following day revealed noticeable improvement in the uptake of OIH but still no excretion. On postoperative day 15, fever and tenderness over the transplant was again noted and treatment for rejection was resumed. Repeat scans revealed decrease in OIH uptake despite treatment. This

*Previously reported case.¹⁸

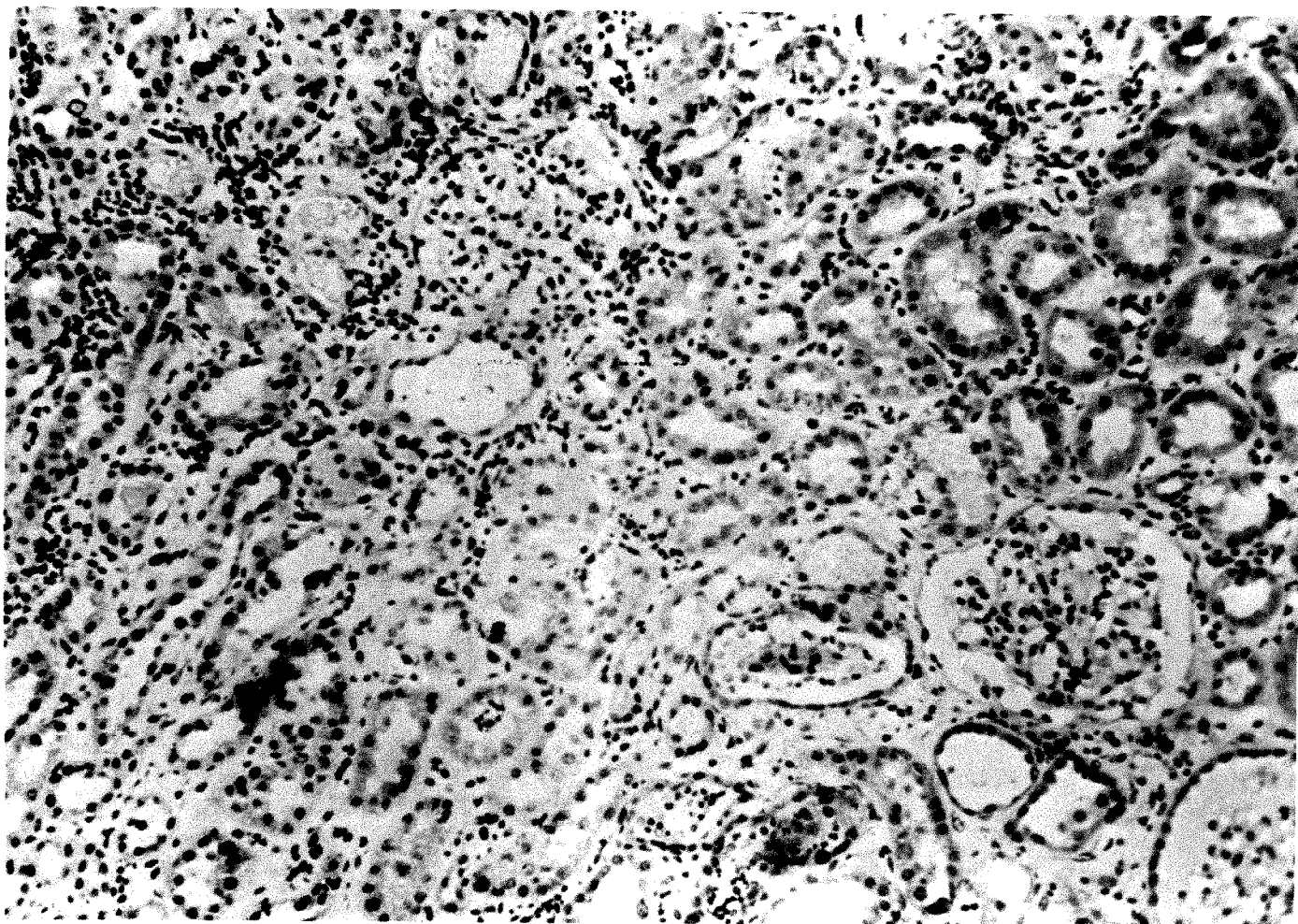


FIG. 10. Photomicrograph of representative section of renal biopsy material demonstrating small round cell interstitial infiltrate consistent with mild rejection, and tubular changes compatible with ATN.

led to an open biopsy on postoperative day 25 which revealed findings consistent with rejection and resolving ATN (Fig. 10).

As a result of the scans and biopsy the kidney was left in place to improve its function. By the time of this patient's discharge, on postoperative day 51, his creatinine was 1.9 mg%.

A repeat scan at 160 days post-transplant showed normal uptake of OIH with rapid accumulation in the bladder.

Discussion

Despite significant advances in the care of patients undergoing cadaver renal transplantation, it remains difficult to appraise function and diagnose the complications of the transplant in the immediate postoperative period. Delayed or inadequate treatment of acute rejection because of the difficulty of interpreting changes in urine output, fever, and leukocytosis during this period allows a significant number of potentially salvageable kidneys to

be permanently damaged or lost.¹ Overtreatment of ATN as rejection, or overtreatment of rejection not responsive to steroid treatment leads to misuse of large doses of steroids with attendant complications.¹⁰

Selected cases from our patient population have been presented to illustrate the use of radionuclide imaging, in conjunction with the clinical course, to evaluate the functional status of the kidney. Serial scans are obtained on all transplants beginning on the first postoperative day. If there is minimal functional abnormality with prompt improvement and good urine output, then the initial delay in uptake and excretion of OIH is attributed to a very mild ATN secondary to cadaver kidney procurement, and immunosuppressive therapy is kept to a minimum. Severe oliguria and the absence of clinical signs of rejection 24 hours after transplantation leads to the presumptive diagnosis of severe ATN. Although an abnormal scan will be obtained, a definite image excludes vascular compromise. The diagnosis of ATN is substantiated by serial scans on subsequent days, which should be static or

demonstrate progressive improvement in the ability of the transplant to take up and excrete the OIH. Immunosuppressive treatment can thus be kept to a minimum, despite persistence of oliguria.

A critical assumption in this interpretation of radionuclide imaging is that the damage from the procurement and preservation of cadaver kidneys is completely manifested on the scan obtained 24 hours after transplantation. Any subsequent deterioration of the OIH image can then be considered secondary to rejection, or to vascular or urinary tract complications. These phenomena are recorded in the surgical literature from broad clinical experience,^{13,19} but to our knowledge have not been studied critically in the laboratory.

One of the most practical uses of the OIH studies has been in the diagnosis and management of severe acute rejection. Since the pathophysiology of kidney rejection consists of interstitial edema, lymphocytic infiltration, platelet sludging and eventual decrease in renal blood flow, one would expect concomitant deterioration in the uptake or excretion of OIH.⁵ The diagnosis of rejection leads to a trial of aggressive treatment. If further deterioration of the OIH image continues during such treatment, early renal biopsy is performed to determine viability of the graft and the necessity for cadaver nephrectomy before complications of steroid therapy become manifest. Serial scans, which demonstrate improvement in the oliguric patient, have allowed us to use high doses of steroids for as long as 7 to 10 days and determine when such treatment can be discontinued.

An interesting phenomena, which we as well as others have noted, is that the scan can reflect acute rejection at a time when the patient is clinically doing well, or the abnormal scan can be coincident with rejection or even become abnormal after a clinical rejection crisis.^{5,9,12} In those cases in which the scan becomes abnormal antecedent to clinical rejection, prompt treatment with high dose steroids may reverse the rejection reaction before irreversible damage has occurred.

The identification of acute rejection superimposed ATN is the most difficult diagnosis of all. This diagnosis is based on the assumption that progressive deterioration of the OIH image after 24 hours is not secondary to ATN, but represents an added insult such as superimposed rejection.

Conclusion

Radionuclide imaging with OIH has contributed to the early diagnosis and appropriate treatment of ATN, rejection, and rejection superimposed at ATN.

It is mandatory to obtain a baseline scan at 24 hours after transplantation in order to interpret subsequent changes.

Radionuclide imaging has identified the patient with

ATN, so that overenthusiastic treatment with massive doses of steroids for acute rejection have been avoided.

Serial studies have allowed early recognition of acute rejection in the non-oliguric patient and have identified transplants which needed to be treated aggressively to reverse severe rejection.

Serial OIH studies in the oliguric patient have allowed the recognition of rejection superimposed on ATN and have allowed us to monitor the effect and duration of treatment for rejection.

In the complex clinical setting of renal transplantation, the value of radionuclide scanning to physicians seems to us to have been clearly demonstrated.

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DISCUSSION

DR. ROBERT JONES (Durham, North Carolina): Dr. Johns, I'd like to compliment Dr. Johnson and his colleagues on the presentation of these well-studied patients, emphasizing the importance of sequential radionuclide measurements of renal function in the management of patients after renal transplantation.

We have recently reviewed similar studies in 50 patients at Duke, and have also been impressed with the importance of these techniques for objective quantitation of function in the transplanted kidney. One patient which illustrates the type of rejective information available from these studies was a 37-year-old man who developed acute rejection in a kidney transplanted from a living related donor into the right iliac fossa.

Persistent deterioration of function in this kidney led to placement of a second kidney from a cadaveric donor in the right iliac fossa. (Slide) This study, obtained three days after the placement of the second kidney, demonstrates very poor hippurate uptake in the right kidney, and good uptake in the left kidney, which is best appreciated after the bladder is evacuated. Quantitation of function by hippurate shows very slow uptake and no excretion in the right kidney; prompt uptake and excretion by the left kidney. The right kidney was subsequently removed, and the left kidney has continued to function well.

(Slide) In addition to the hippurate study, we routinely perform sequential perfusion studies, using sodium pertechnetate. Following an intravenous bolus of 15 millicuries of this agent, the area over the transplant is sequentially imaged at two-second intervals. As the bolus arrives, the aortic bifurcation and the iliac arteries are seen, and then on subsequent films, in the absence of vascular obstruction, the kidney appears.

Although the initial uptake of hippurate should reflect perfusion in patients with severe rejection, the hippurate may be concentrated so poorly that one cannot be certain that perfusion is present. In our study of 50 patients we found two where we could not be certain with the hippurate study, and in those cases this technetium study was useful to determine that the kidney was indeed perfused.

DR. ARNOLD G. DIETHELM (Birmingham, Alabama): Oliguria or anuria following renal transplantation requires early analysis and decision if intervention with the appropriate patient management program is to be successful. Acute tubular necrosis, acute rejection, obstruction of the renal vascular anastomosis, and ureteral obstruction all may cause impaired renal function in the immediate posttransplant course. Renal arteriography, intravenous and retrograde pyelography, and renal biopsy all provide specific data which may be of help in the investigation of the underlying problem. However, with the exception of the IVP, the other techniques are invasive in type, and not without complications of their own.

Radionuclide investigation of the posttransplant kidney, as described by Dr. Johnson and Dr. Mandel, provides an additional approach in the analysis of renal allograft function. At the University of Alabama we have performed 420 such investigations in ninety patients posttransplantation, combining several parameters, including the renal scan, the renogram, estimated renal plasma flow, and the excretion index of the isotope injected.

(Slide) This demonstrates the calculations involved. The estimated renal plasma flow, noted as ERPF, can be calculated by the renal clearance of orthiodo-hippurate per minute, with the normal flow greater than 250 ml per minute. The predicted excretion in terms of percent can be plotted minutes after the injection. As you can see, the disappearance of the hippurate from the blood depends upon renal function, and the excretion is a function of the estimated renal plasma flow. The excretion index, as noted here, is the total amount of dye excreted divided by the predicted excretion, giving a normal value of 0.8 to 1.2.

(Slide) This demonstrates both the estimated renal plasma flow and excretion index on the graph. Patients with normal values include an ERPF greater than 250 ml, and an excretion index greater than 0.8. Individuals with acute rejection have both a decreased excretory index and ERPF. Patients with incomplete ureteral obstruction have a normal ERPF but a decreased Excretory Index, and patients with acute tubular necrosis have a markedly decreased excretory index with a slightly decreased ERPF.

This approach provides an opportunity to analyze renal function in

posttransplant patients and to place a specific number on their excretory index and estimated renal plasma flow.

Renal artery obstruction, of course, shows no isotope uptake by the kidney at all. In summary, radionuclide imaging provides a noninvasive, reproducible approach to the analysis of renal tubular dysfunction in the posttransplant period which can be expressed using a specific numerical value.

I would like to ask two questions. First, have you studied patients with either accelerated or chronic rejection, and how has this information been of help in the diagnosis and management of that particular problem? Second, what has been your experience in the diagnosis of impending rejection before alterations in the serum creatinine and BUN occur, and has the use of the scan been able to predict this event?

DR. LESLIE E. RUDOLF (Charlottesville, Virginia): I thoroughly enjoyed this paper by Dr. Johnson, and want to congratulate the author on what I think is a most useful procedure, particularly for dealing with patients who are recipients of cadaver kidneys, particularly cadaver kidneys that have been preserved for long periods of time.

I have three questions for them. One of them approximates Dr. Diethelm's question, and that is: Have you done any scans on patients before the 24-hour period of time? Certainly some of the kidneys that we are exchanging, at least in the Southeastern Regional Organ Donor Program, have been subjected to a period of hypothermic preservation—that is, just placed on ice. Then some have been perfused and put back on ice, and shipped to various institutions. I must admit that many of these kidneys we put in do not work right away. We may get a little more nervous than the people do in North Carolina, and wonder what's going on before the 24-hour period of time is up. So the questions is: Might an early scan prove a useful tool before the 24-hour period of time?

Secondly, having had the opportunity to read this paper, I would like to question the following concept: Is the amount of damage that occurs to the preserved kidney really totally manifest at the end of the 24-hour period, and what about the kidney that's recovering from ATN—might not this injury go on for a period beyond 24 hours? I think this is really an important question.

The last question is a hard one, because I think all of us preserving kidneys for any period of time are really groping for methods of predicting viability of some of these organs during their course of preservation. Certainly, we have transplanted a few kidneys that during preservation looked good by all parameters—systolic pressures, diastolic pressures, and so forth—and, unfortunately, one or two of these kidneys have proved to be nonviable on subsequent biopsy.

Have you given any thought to scanning this kidney while it's being perfused as an index of subsequent function? This is a difficult problem, because you cannot use a recirculating circuit and you must have one-pass perfusion. I think this might be a very interesting study and possibly a useful approach to this problem.

DR. STANLEY R. MANDEL (Closing discussion): In regard to Dr. Diethelm's question about the scans in accelerated rejection, we have found it very helpful in the treatment of these people. If you embark upon a course of aggressive immunosuppressive therapy, which has a series of complications, we like to use the scan to see whether or not we're making progress as we continue to inject large doses of steroids. It therefore has been helpful to see where we're getting in treating accelerated rejection.

As far as chronic rejection, this is frequently a diagnosis made on biochemical grounds; but we have had people who have come in with what looked to be a chronic rejection, with a rise in BUN, a rise in creatinine, and a drop in urine output, and we have gotten a scan, and to our surprise on a couple of occasions, we have found some unsuspected diagnoses, such as lymphoceles, which were obstructing the ureter, and which were easily treated by incision and drainage, rather than another massive dose of immunosuppression. The scan has been very helpful to us in both accelerated and chronic rejection.

One of the most interesting aspects of the use of the scan to us has been that very commonly the scan will reflect rejection before it becomes apparent clinically. We have enough confidence in the scan so that the patients who have an abnormal scan suddenly appear are treated even though the BUN and creatinine have not started to rise. In our experience this frequently occurs, and then about two or three days

later you get the overt biochemical changes of rejection. I think it has allowed us to save some kidneys that might otherwise be lost from rejection.

In regard to Dr. Rudolf's question, we always get the scan at 24 hours, but there have been occasions when we have gotten it before 24 hours. If you are faced with a patient who suddenly becomes oliguric, then it raises a question about whether or not a sudden vascular occlusion has occurred, and we would go on and get the scan that night in the immediate postoperative period. It's my personal opinion that if you pick up vascular occlusion immediately, particularly venous occlusion, you can save the kidney, even if two or three hours have passed. We have had personal experience with an embolus from the leg that went up to the iliac vein and blocked off the renal vein, the patient became suddenly anuric, and experienced pain over the kidney, and we got a scan which showed no vascular perfusion. I knew there was something going on in the vascular system, so we operated, and found an embolus lodged at the anastomosis of the renal vein to the iliac vein. Even though the vein was completely occluded, there was some arterial perfusion, but not enough to pick up any hippurate.

We pushed the embolus back down into the leg, ligated the distal iliac vein and the kidney went through three weeks of ATN which we followed with the scan, and then completely recovered. The patient has gone home with normal renal function.

One of the key assumptions in utilizing scans is the one that Dr. Rudolf just brought up, and which we were very worried about and brought up in the paper. In order to interpret this work, and in order to really believe in it, you have to believe that the changes and damages of

procurement of cadaver kidneys is established at the end of 24 hours. To my knowledge, this has not been studied in the laboratory, and we are now in the process of doing this. The assumption has been made on the basis of a large clinical observation. Several large series have observed this, and we have observed it in our patients. It seems logical that ATN in cadaver preservation is established at 24 hours, but I'm not sure that that's absolutely true, because it's never been studied. At least clinically, we have been able to utilize that assumption, and we admit it's an assumption, but others have made it, and it seems to have worked clinically.

I don't know how you would use the scan to determine viability of the kidney, Dr. Rudolf, but I suspect that with some further work that would be a possibility.

I would like to summarize by pointing out that it is not the scan as an isolated procedure that is so important, but, rather, a distinct protocol which allows you to serially follow the changes that occur. The first scan must be taken at 24 hours, and subsequent scans are utilized to diagnose ATN, diagnose rejection, allow for treatment, allow you to monitor what you are doing with your therapy. I think if you use it this way, it will be a very useful clinical tool. It allows you to be out on the ocean with a map, and at least know what direction you are going in, and, I think, accurately diagnose what you are doing. In these people the margin is so narrow between overtreating them with steroids and getting into trouble or undertreating them and allowing them to reject, that I really think you can improve your patient care tremendously by utilizing the radionuclide scans.

Hypertension Due to Renal Artery Stenosis in Transplanted Kidneys

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E. STEVERS GOLLADAY, M.D., JOHN C. McDONALD, M.D.

Hypertension appeared to be related to stenosis of the hypogastric renal artery system in 5 patients among 153 recipients of renal allografts. Renin assay and arteriography were crucial in the comprehensive evaluation of patients whose hypertension was not clearly related to rejection or excessive sodium intake. Hyperreninemia was persistent in 4 of the 5 patients. Stenoses of the transplant renal arteries in three patients were caused by extensive intimal plaque formation. In one patient, periarterial fibrosis caused reduction of flow; 180° torsion of the anastomosis resulted in stenosis in the fifth patient. Surgical correction is difficult and may be facilitated by a transabdominal approach. Vein bypass is probably preferable to patch angioplasty for intimal lesions. Following operation, hypertension was ameliorated and function improved in all patients. Rejection, which has been suggested as one of the causes of intimal plaque formation, ultimately led to the loss of the transplant in one patient. Function is normal in two patients; two patients have evidence of chronic rejection. No effort should be spared to evaluate this special group of patients whose transplant function can predictably be prolonged by decisive surgical management.

HYPERTENSION and deterioration of renal function in recipients of renal allografts require careful evaluation to precisely establish the causes of such crises. Five patients, among 153 transplant procedures in our experience, have been found to have significant stenoses of their hypogastric-renal artery systems which seemed to contribute to the development of severe hypertension. Four of these patients were alluded to in an earlier publication¹⁶ dealing with the general problem of hypertension and hyperreninemia in transplant recipients.

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Materials and Methods

One hundred fifty-three transplantation procedures have been performed in 128 patients. Retrograde iliac arteriography was performed in 36 of this group, including the 5 who are the subject of this report. All 5 patients had end-to-end hypogastric artery to renal artery anastomoses. Four patients received kidneys from related donors; one received a kidney from a cadaver donor.

Sixty-eight renin determinations were performed in the 5 patients; 24-hour urinary sodium excretion was measured at the time of each renin assay. All renin assays presented were determined from peripheral venous blood. Bioassay for renin concentration, as previously reported,¹⁶ was performed according to the method of Gould, Skeggs and Kahn.⁷ Radioimmunoassay,⁸ reported as plasma renin activity (PRA), was performed using the standard method of the Squibb Angiotensin I Immutope[®] Kit, using a 3-hour incubation. PRA is recorded as nanograms per milliliter per hour (ng/ml/hr) of angiotensin I activity.

During the time required for this study, our laboratory switched from the use of bioassay for renin determination to the use of radioimmunoassay. Correlation of the two methods was evaluated by determination of renin levels, using both techniques, in 31 randomly selected volunteers. Paired samples were drawn simultaneously. The

TABLE 1 Patient Number 1: Transplant 8/31/71,
Arterial Revision 7/2/73

Time After Transplant (Mon)	Blood Pressure mmHg	Serum Creatinine mg%	24 Hr Urine Na+ meq	Plasma Renin Activity (PRA)
9	150/84	2.0	95	2.41
19	170/110	2.3	78	3.07
21	190/120	2.7	68	8.53
22**	190/130	4.0	84	7.21
22½	126/76	1.7	57	2.41
24½	140/90	2.1	106	1.61
38½	140/80	2.1	100	2.40

** Arterial Revision

correlation coefficient between the bioassay and the radioimmunoassay was determined to be 0.91 ($P \leq 0.01$); further analysis showed the F value to be 137.09 ($P \leq 0.01$). Thus, the two methods yield comparable results. Such comparison of renin assay methods has been supported by others^{4,10} but must be done by each laboratory to ensure accuracy. For the purpose of this report, therefore, renin levels determined by bioassay have been converted from Goldblatt units/ml to ng/ml/hr of angiotensin I activity (PRA) by using the regression equation determined for this laboratory. Such values are indicated in the tables by (*).

Results

Each table chronologically displays blood pressure, serum creatinine, 24-hour urinary sodium, and PRA. All

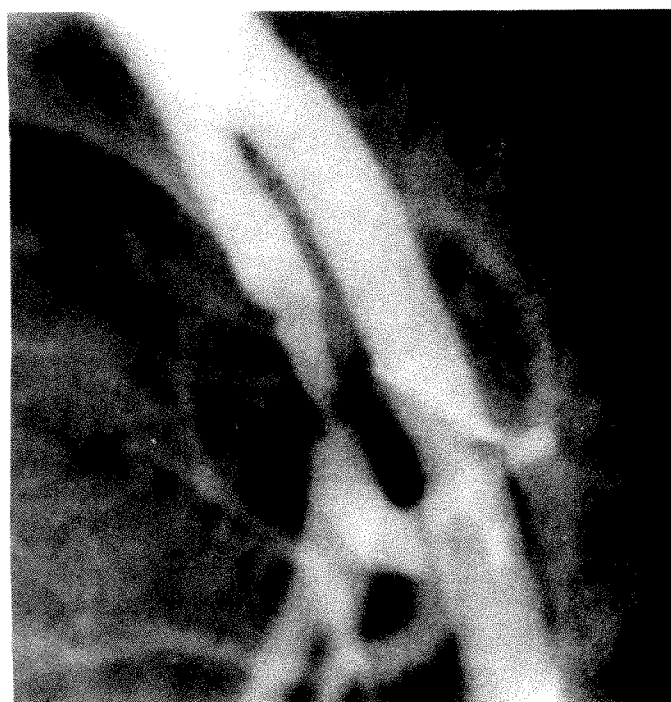


FIG. 1. In Patient No. 1, stenosis began in the left hypogastric artery and extended to just proximal to the bifurcation of the renal artery.

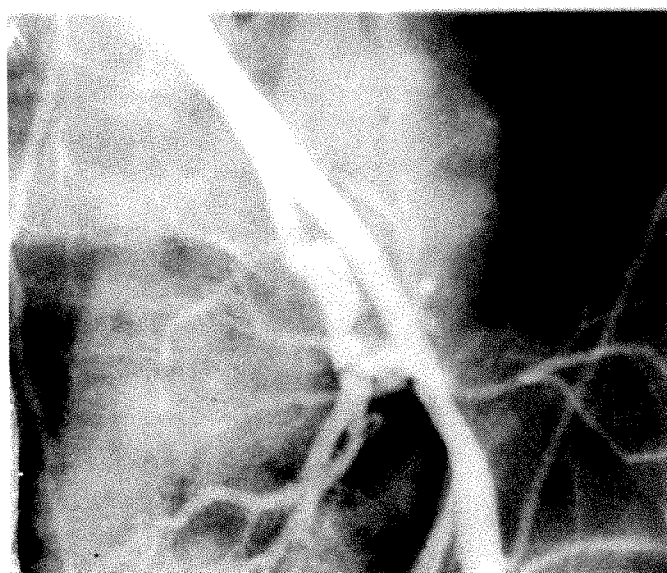


FIG. 2. In Patient No. 1, following operation, ballooning of the vein patch can be seen. Linear area of nonopacification probably marks the distal suture line.

patients were taking potent antihypertensive agents at the time of correction of the stenoses of their transplant renal arteries.

Patient No. 1: (Table 1) A 26-year-old man received a kidney from his sister. PRA elevation preceded hypertension by 9 months. Arteriography (Fig. 1) showed a high-grade stenosis. The failure of intensive medical management to control the hypertension and the deterioration of renal function led to operation. An extensive plaque, beginning 1 cm proximal to the arterial anastomosis and extending 3.5 cm distally, was identified. There was no palpable distal pulse, and a 1.5 mm probe could not be passed through the stenotic segment. Vein patch angioplasty was done. Major deep wound infection delayed recovery. Arteriography 6 months postoperatively (Fig. 2) shows what may be a "web" in the distal margin of the vein patch. Since the patient presently requires no antihypertensive drug, no further surgery is

TABLE 2 Patient Number 2: Transplant 6/5/73,
Arterial Revision 8/2/73

Time After Transplant (Mon)	Blood Pressure mmHg	Serum Creatinine mg%	24 Hr Urine Na+ meq	Plasma Renin Activity (PRA)
1	160/104	1.2	84	1.13*
2**	180/120	5.7	274	1.05*
3	124/78	3.8	73	1.44*
4	160/110	3.5	80	0.95*
5½	110/90	4.8	50	1.38*
9	140/110	3.6	34	1.90
17½	130/100	3.9	80	1.90

* Estimated PRA

** Arterial Revision

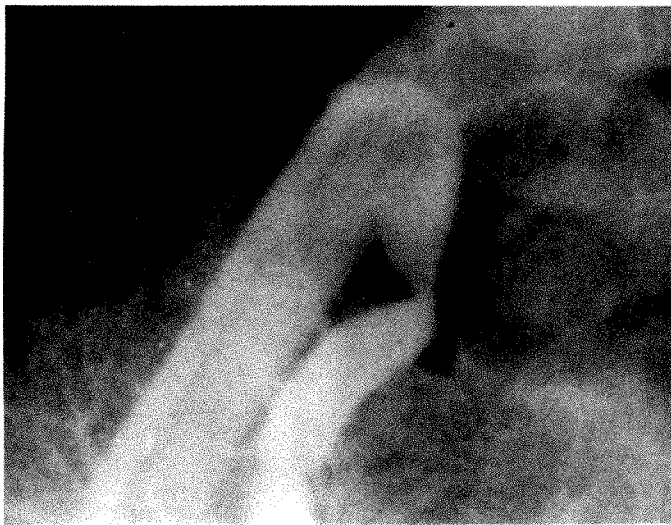


FIG. 3. Symmetrically tapered defect in Patient No. 2 marks torsion of the anastomosis.

planned although it is noted that both PRA and creatinine are modestly elevated.

Patient No. 2: (Table 2) Two months after he had undergone bilateral nephrectomy, a 26-year-old man received a kidney from a cadaver donor. Disruption of the ureteral implant required ureteroureterostomy. Severe hypertension developed early after transplantation, leading to arteriography (Fig. 3). One hundred eighty degree torsion of the hypogastric-renal artery system was corrected by resection of the twisted segment and reanastomosis of the vessels. Hypertension has been manageable with diuretics alone since operation, but there appears to be progressive rejection, characterized by rising creatinine, persistent proteinuria, and elevated PRA in the presence of normal arteriography.

Patient No. 3: (Table 3) Four months after receiving her brother's kidney, this 16-year-old girl became severely hypertensive and had hyperreninemia. Retrograde iliac arteriography demonstrated (Fig. 4) an extensive, irregular area of stenosis. Vein interposition replaced the distal hypogastric artery and the entire renal artery to its

TABLE 4. Patient Number 4: Transplant 5/15/73, Arterial Revision 10/10/73

Time After Transplant (Mon)	Blood Pressure mmHg	Serum Creatinine mg%	24 Hr Urine Na+ meq	Plasma Renin Activity (PRA)
0	140/90	8.0	—	1.52
4½	190/110	2.4	112	2.99
5**	126/90	2.3	58	—
12½	170/110	2.0	94	5.03
15	200/120	2.8	30	6.35
16½	190/110	3.7	42	—
18***	150/106	6.5	—	1.33 ⁺

** Arterial Revision *** Transplant Nephrectomy

⁺ 2 days post-nephrectomy

bifurcation. The plaque appeared to arise just distal to an umbilicated defect on the posterior aspect of the intima of the hypogastric artery, representing the stump of a large presacral branch. The patient presently takes furosemide, 120 mg daily.

Patient No. 4: (Table 4) A 30-year-old man received a kidney from his brother. Within 4 months, severe hypertension and moderately elevated PRA were noted. Arteriography (Fig. 5) showed severe stenosis which, at the time of vein interposition (hypogastric artery to distal renal artery), was found to arise just distal to the original anastomosis. Kidney biopsy showed marked hypertrophy and granulation of the juxtaglomerular apparatus (Fig. 6). Also seen were scattered areas of round-cell infiltration and numerous small arteries with subintimal proliferation, compatible with mild rejection. Following relief of the arterial stenosis, blood pressure was easily controlled, but only for 6 months. Repeat arteriography demonstrated a widely patent artery. At this time, extreme hyperreninemia was demonstrated, by selective

TABLE 3. Patient Number 3: Transplant 3/13/73, Arterial Revision 9/2/73

Time After Transplant (Mon)	Blood Pressure mmHg	Serum Creatinine mg%	24 Hr Urine Na+ meq	Plasma Renin Activity (PRA)
4½	160/120	1.0	91	1.24*
5	172/136	1.3	72	1.38*
5½**	170/130	1.3	104	3.60*
6	190/130	1.2	222	2.36*
10	130/90	1.2	64	0.42
14½	126/96	1.4	103	1.04*
20	130/90	1.0	110	0.38

* Estimated PRA ** Arterial Revision

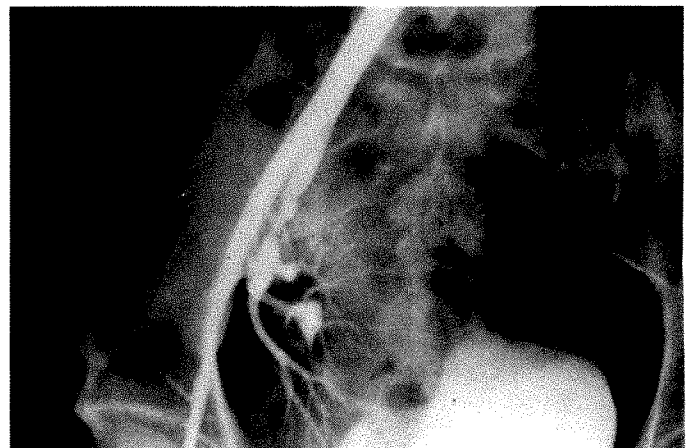


FIG. 4. In Patient No. 3, prior to vein bypass, the extensive lesion began just distal to ligated branch of hypogastric artery.



FIG. 5. Short segment of stenosis in Patient No. 4 was confined to the renal artery. Such a defect might be obscured by superimposition of the external iliac artery (See Discussion).

venous sampling, to arise from the allograft. Aggressive treatment for rejection failed to modify the progressive renal failure. Antihypertensive drugs, including minoxidil, failed to control the hypertension and were not tolerated well by the patient. Transplant nephrectomy was followed by marked decline of PRA and conversion of the hypertension to the "volume dependent" type.

Patient No. 5: (Table 5) This 38-year-old citizen of Columbia, South America received his transplant from a sister but was compelled to return 9 months later for evaluation of hypertension. At operation, the cause of the stenosis of the proximal hypogastric artery seen on arteriography (Fig. 6) was found to be dense periarterial fibrosis. No distal pulse could be palpated beyond the extrinsic stricture until the artery was liberated. Blood pressure is now easily controlled with low doses of furosemide and methyldopa.

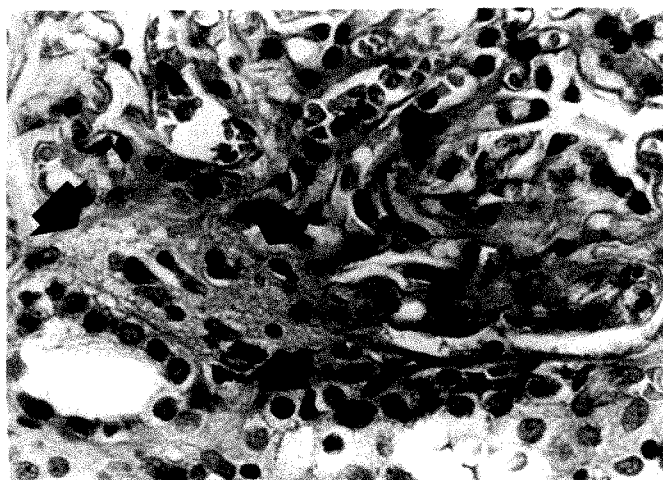


FIG. 6. Biopsy from Patient No. 4 at the time of vein bypass. Immediately to the left of the glomerulus can be seen the cluster of hypertrophied cells of the juxtaglomerular apparatus.

TABLE 5. Patient Number 5: Transplant 2/22/73, Arterial Revision 11/27/73

Time After Transplant (Mon)	Blood Pressure mmHg	Serum Creatinine mg%	24 Hr Urine Na+ meq	Plasma Renin Activity (PRA)
9	140/110	1.1	47	6.54
9½**	180/120	1.5	94	6.40
10	190/120	0.7	143	0.47
10½	140/100	1.1	85	0.69

** Arterial Revision

Discussion

Renal allograft dysfunction, mysterious as it often appears, is usually susceptible to rational analysis. Standard biochemical assessment of renal function, excretory urography, cystography, radionuclide renography, and arteriography are now complemented by radioimmunoassay of PRA. Xenon washout studies of renal blood flow require expensive equipment and selective injection of radioisotope into the renal artery; furthermore, it is doubtful that the information derived is any more useful than that from simpler techniques for estimation of renal blood flow using technetium tracers.

Recipients with declining renal function should not be assumed to have rejection inasmuch as the syndrome can be mimicked by renal underperfusion due to stenosis of the principal artery.^{13,21} Patients 1 and 2 in this study had serious impairment of renal function at the time of secondary arterial surgery; significant improvement followed correction of the stenoses. Failure of revascularization to restore completely normal function in 3 patients has been



FIG. 7. The nonopaque "band" at the origin of the hypogastric artery in Patient No. 5 was due to periarterial fibrosis.

ascribed to progressive rejection, but the theoretical "vasculotoxic" effect of renin^{12,15} cannot be excluded. Chrysant and associates⁵ have suggested that potential recipients with hyperreninemia arising from their autologous kidneys should have prophylactic bilateral nephrectomies to minimize the hazard of potential hypertensive injury of the transplant.

Denervated renal allografts can respond with renin production, much in the fashion of a normal kidney, when flow declines as a result of standing or of volume depletion.^{1,6,20} The corollary of this phenomenon is that hyperreninemia may follow any reduction of renal blood flow, such as might occur with acute reversible ischemia, stenosis of the renal artery, or extensive intimal lesions of segmental and more distal renal arteries. PRA elevation in the first few days following transplantation^{1,19} may be due to the same ischemic injury responsible for tubular necrosis.¹⁹ Beckerhoff and associates¹ have suggested that the variable orthostatic effect on renin levels in transplant patients may be related to position of the graft in the iliac fossa. Although a rise in PRA during the first few days following transplantation is not prognostically important, elevation of the enzyme beyond this time seems to be associated with more severe dysfunction.^{16,19}

Transplant nephrectomy in Patient No. 4 dramatically relieved the severe hypertension which was clearly "renin dependent." Chrysant and associates⁵ recently reviewed the concept that "multiple Goldblatt clamps" may be simulated in a renal allograft undergoing rejection. Rejection and hyperreninemia do not, however, necessarily go hand in hand. Such a paradox may, as proposed by Kurtzman and associates,¹¹ be explained by temporary conversion of the hypertension from "renin dependence" to "volume dependence." In this sequence,¹¹ initial hyperreninemia leads to sodium retention which ultimately results in volume expansion; as underperfusion is temporarily ameliorated, renin release is inhibited. Sampson and associates²⁰ have proposed that post-transplant hypertension does not depend upon renin but rather upon corticosteroids which might be converted to aldosterone. An alternative explanation of low PRA during rejection is that the juxtaglomerular apparatus are neutralized by mononuclear cell infiltration.

Blaufox and his associates³ found in 7 transplant patients no association between hyperreninemia and hypertension. Our earlier studies in 35 transplant recipients,¹⁶ on the other hand, demonstrated in the group as a whole a significant positive relationship between renin levels and hypertension. Nevertheless, hypertension in transplant patients is a complex process. Some patients with hypertension were found to have low levels of PRA whereas a few normotensive patients had very high levels of PRA.

Careful auscultation over the iliac fossa for bruits related to flow in the transplant artery has been practiced

regularly on our service since Jachuck and Wilkinson⁹ reported their experience. These authors suggested that bruits which persist for more than two months usually presage the development of hypertension, but we have found a number of normotensive patients to have bruits. More clinical experience will be required to fully evaluate the implications of such a subjective observation.

Selective catheterization of the hypogastric artery for transplant arteriography has been condemned¹⁸ because of the hazard of dislodging plaques or of causing subintimal dissection. For this reason, we have contented ourselves with injection into the common iliac artery; no complication has resulted from this approach. If any of the hypogastric-renal artery system is obscured by the external iliac artery, a positional adjustment must be made for the second sequence of films.¹⁸ We have been particularly impressed by the discrepancy between the real caliber of the stenotic segment found at operation and the "apparent" lumen size,¹⁷ a magnification artifact of tube-patient-plate distances, seen on arteriography.

Occlusive lesions of the transplant renal artery may be classified and characterized broadly as follows: 1) Malrotation; 2) Extrinsic (a) Severe periarterial fibrosis (b) Kinking; 3) Intrinsic (a) Arising in recipient artery (b) Arising in donor artery. It is difficult to understand why more transplant arteries are not, in fact, gradually occluded by the extreme fibrosis which results, in all probability, from a combination of peri-iliac dissection and rejection reaction. Margules, Belzer and Kountz¹⁴ summarized the mechanisms which may lead to intimal plaque or granuloma formation. Doyle and his associates, in a study soon to be published, have discussed their findings in 12 patients with stenoses of transplant renal arteries. To these lists of instrumental trauma, technical errors of blood vessel suturing, and allograft rejection, we would add the guess that flow injury (as in Patient No. 3) may sometimes be a significant factor. Prevention of arterial injury at the time of transplantation¹⁴ may be the most important consideration of all. Side-to-end external iliac artery-to-renal artery connections may be more prone to develop anastomotic stenoses than are hypogastric-to-renal artery systems.²

Vein interposition bypass is certainly more tedious than use of a vein patch but is supported by Lee and his associates,¹³ who found occlusive plaques to recur under 3 of 6 patch angioplasties. Patient No. 1 of this series (See Fig. 2) has given us cause for concern; it may yet be imperative to more precisely assess the significance of the nonopaque transverse "defect" seen on arteriography.

Hypothermic protection was provided for the transplant during interruption of blood flow in the cases (Patients 2, 3 and 4) requiring vein patch or vein bypass. After common iliac and external iliac arteries had been controlled, a cannula was placed through a small ar-

teriotomy in the external iliac artery. The renal vein was "vented" while the kidney was perfused using gravity flow. Such precautions may appear excessive, but these operations are comparable in name only to correction of stenoses of the arteries of autologous kidneys. Liberation of the hypogastric-renal-artery system is fraught with the real hazard of shredding the vessel.

Now that renin radioimmunoassay is so rapidly available, it is much easier to evaluate prospective transplant recipients and those who, following transplantation, have difficulty with hypertension or declining renal function. It would be folly, however, to depend upon a single value of PRA, particularly if determined from a peripheral venous sample, when one must make serious decisions regarding patient management. Although "normal" levels of PRA are the subject of dispute and confusion, we have felt that trends of the enzyme level can be most useful. Integration of all data related to renal function, PRA, renography, arteriography, and even biopsy must ultimately lead to the best treatment of these very ill patients.

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DISCUSSION

DR. GARLAND D. PERDUE (Atlanta, Georgia): I would like to generally support the observations of these authors and their conclusions. Our own experience would tend to parallel theirs, with about 4% incidence of delayed occurrence of constriction of the renal artery, and operative techniques being successful in relieving this stenosis and ameliorating what had been intractable hypertension in these patients.

We have also had one patient who developed an angulation of his artery which I believe was due to my technical malfeasance. That was, of course, an early problem, recognized early and corrected.

The most singular observation, I think is that in our patients who had impaired renal function associated with their intractable hypertension, the relief of the arterial stenosis and improvement in tractability of hypertension has been accompanied by improvement in renal function, but not by return to its previous level; so that we have interpreted the lesions that we have seen—which, incidentally, have all been in the donor artery, with perhaps a minimal involvement at the level of the anastomosis itself—as a manifestation of the rejection process, and analogous to the subintimal fibrosis which they have observed in their patient in smaller arteries and in the renal parenchyma itself.

DR. SESHARDI RAJU (Jackson, Mississippi): In Jackson we have had

experience recently with two patients presenting with renal artery stenosis after transplantation.

I'd like to make three points. The first is that a transperitoneal approach for correcting the stenosis is far superior to the extraperitoneal approach. The first patient we did extraperitoneally; the second patient, transperitoneally. There is no question that the transperitoneal approach is far simpler and cuts the operating time by at least ninety minutes.

The second point is to question the value of plasma renin assays as a screening test for this problem. Our endocrinologists are very dubious, because they point out quite rightly that these patients are on salt restriction antihypertensives or on diuretics; they are also on cortisone, all of which are known to affect plasmas renin levels. In our view, arteriography is a better screening method for these patients who present with hypertension after renal transplantation.

The third point, which Mr. McDonald touched upon briefly in his presentation, is the possibility that a so-called discrete stenosis may actually be an early stage of chronic rejection affecting the entire renal arterial system.

(Slide) This renal arteriogram is that of a patient operated on by Dr. George V. Smith and myself. Nearly a month transpired between this arteriogram and surgery. We were surprised to find that the lesion was far more extensive than was indicated by the arteriogram, apparently because chronic rejection had progressed.

Of course, there are other reasons for transplant renal arterial stenosis, such as traction injury at the time of donor nephrectomy; also the use of umbilical tape or heavy silk to tie down the perfusion cannula may possibly be responsible for subsequent stenosis. But some stenoses at least may be early manifestations of chronic rejection affecting the arterial system.

DR. KENT JONES (Durham, North Carolina): At Duke Medical Center we have performed a total of 238 renal allograft transplant procedures, and a select number of patients postoperatively have been subjected to arteriography because of persistent hypertension, deterioration in the renal function, or persistent bruit noted over the allograft. We have found a total of six patients who have had significant stenosis within their donor renal artery, four of these patients previously having undergone cadaveric transplant and two being living related donor recipients. I think that these six patients contribute three interesting points to the discussion of this fine paper that has been presented.

Dr. Gunnells and co-authors at our institution first demonstrated that denervation and transplantation of the human kidney did not decrease its ability to produce and secrete renin. We have also found that renin assays are many times a valuable method of selecting patients who are candidates for postoperative arteriographic studies, and that selective vein renins are many times an important method of assay to determine the significance of this stenosis.

Two of our patients, however, have failed to show a correlation between their selective vein renin measurements and their response to subsequent treatment.

(Slide) This patient initially underwent a living related donor transplant. Postoperatively he developed persistent hypertension, and renal arteriography was performed. This shows a normal appearing anastomotic site and donor renal artery.

His hypertension persisted, and renal function continued to deteriorate, and a renal biopsy was performed which showed rejection. About a month later a second allograft from a cadaveric donor was implanted into the opposite pelvis. Postoperatively he again developed hypertension, and renal arteriography was again performed, demonstrating a fairly significant stenotic lesion in the cadaveric donor artery and thrombosis of the renal artery to the living related donor graft. Selective renal vein renin measurements showed 1000 ng% from the living related donor vein and 1500 ng% from the cadaveric renal vein.

A nephrectomy of the thrombosed, rejected living related donor graft was performed, and presently the patient is normotensive, with normal renal function on antihypertensive medication. He has had an IVP which shows normal renal function.

The second patient is a girl who postoperatively developed intractable hypertension with a deterioration in renal function, and again showed a marked stenosis of the donor renal artery. She subsequently had selective renal vein renins which showed fairly equal values from both of her autologous kidneys, as well as a selective renin from the transplanted kidney of about 400/ng%. Both of the autologous kidneys were removed with no change in her deteriorating course.

The second point which I would like to make is that, of the six patients in whom we have found significant stenosis by arteriography, only three have had chronic hypertension or an alteration in renal function, demonstrating the ability of the allograft to function quite normally in many cases in spite of marked vascular occlusion.

(Slide) This patient had a cadaveric donor graft inserted and post-

operatively became hypertensive. This arteriogram was performed again demonstrating marked stenosis. At the present time he is normotensive on antihypertensive medical therapy, has normal renal function, and a normal intravenous pyelogram.

(Slide) This is the second patient, who had a living related donor graft implanted, and postoperatively was noted to have a bruit over the graft. The study we performed showed a significant stenosis, but he too normotensive on medical therapy, with normal renal function and a normal intravenous pyelogram. We have found that in some of these patients it is possible to treat them with medical therapy, and they will respond favorably and avoid the reoperation which we, as the authors have found to be a difficult procedure, due to the marked perioperative fibrosis.

The third point I would like to make is that we too have noticed what has been described, or alluded to, in this paper, and also described by the gentleman from Atlanta. All six of our patients have had stenosis, not at the anastomotic site, but within the donor renal artery distal to the anastomosis. This was first described by the group at the Medical College of Virginia, and is a significant finding.

In conclusion, I would too like to congratulate the authors on a most interesting and informative presentation, and would like to close by asking them what their incidence of distal stenosis within the donor vessel has been.

DR. EDWARD S. LINDSEY (Closing discussion): May I respond first to Dr. Perdue? Certainly, kinking has been recorded by a number of other authors, and is worthwhile keeping in mind, particularly when one uses long donor arteries or has an hypogastric artery of excessive length. Failure of the function to return to normal may be the clue to the suspicion that arterial stenosis goes hand in hand with some sort of severe rejection process in some cases.

I would agree now with Dr. Raju that the transperitoneal approach has great merit. Indeed, these are very difficult operations, as you who have been there know.

The usefulness of the renin assay is a real can of worms. I hope you understand from my presentation that we did not depend exclusively, by any means, on renin assays. As a matter of fact, you will note that one of the patients (No. 2) had quite normal renin levels.

Dr. Jones, we appreciate your fine discussion of this. The question of bruits is a difficult one to settle. Jachuck and his associates some years ago reported this phenomenon in transplants. We have been very careful to follow our transplants by listening for bruits, and have found normotensive patients with very bothersome bruits, and hypertensive patients with no bruits at all. So I don't know yet what to make of it.

I would insist again that serial renin levels are more useful than random single assays. With respect to the segmental nature of renal artery stenosis, you showed, Dr. Jones, in one of your arteriograms what I think might be stenosis of the secondary renal arteries. Certainly segmental arterial stenosis causing renin dependent hypertension has been well described.

Our patients are a mixed group in terms of the level of the stenosis. Two of them had lesions beginning clearly in the donor artery, one in the recipient artery as well as the donor artery; the remaining two were technical problems altogether, with torsion and periarterial fibrosis.

In conclusion we would like to suggest that the problem of hypertension and declining renal function in the allograft recipient is a rather complex one, but in any case one which requires aggressive treatment in selected patients.

An Analysis of Twenty Years' Experience with Operations for Carcinoma of the Stomach

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We analyzed the records of 242 consecutive patients with adenocarcinoma of the stomach operated on for cure. We correlated survival with several factors, including the type of primary lesion, the operation performed, operative mortality, state of regional lymph nodes, margins of the resected specimens, and duration of preoperative symptoms. Overall survival at 5 years was only 18.6% and at 10 years was 7.1%. Patients with small malignant gastric ulcers, however, enjoyed increased survival at 5 years (53.8%) and at 10 years (15.0%). Overall operative mortality was 7.1%, but was 0% for patients with small malignant gastric ulcers. Even with large or high-lying lesions, radical operation can be accomplished with acceptable mortality and definite chance for cure. Thirteen of 45 five-year survivors had positive lymph nodes, and 7 of the 45 had positive margins of resection. Longer symptomatic preoperative periods correlated positively with increased survival. Thirty patients with preoperative symptomatic periods exceeding 24 months had a 30.0% 5-year survival. Perhaps some of these lesions underwent malignant change in areas of symptomatic benign disease. We advocate early operation for gastric ulcers which do not heal promptly and stay healed.

TWENTY-TWO YEARS AGO, before this Association, I. S. Ravdin and R. C. Horn⁶ reported on the results of 193 gastric resections for carcinoma of the stomach performed at the Hospital of the University of Pennsylvania. This early series included 37 small gastric ulcers that were histologically malignant. Ravdin and Horn proposed that some of these gastric cancers arose in areas of primary benign ulceration, and they urged early operation for small gastric ulcers that did not quickly respond to intensive non-operative therapy. To evaluate these conclusions further we have analyzed our subsequent experience with adenocarcinoma of the stomach resected for cure.

Patients with "small malignant ulcers" were segregated for comparison with the residual group of patients with "other adenocarcinomas" of the stomach. In addition to size of lesion, we have evaluated other factors that

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seem to influence survival. Specifically, we reviewed the surgical procedure performed, operative mortality, presence of lymph node invasion, state of resected margins, and duration of preoperative symptoms.

Clinical Material

This report is based on the entire experience at the Hospital of the University of Pennsylvania with histologically verified gastric adenocarcinoma resected for cure from January 1, 1953 through December 31, 1966. All patients have been followed through December 31, 1973. The experience includes patients operated on by surgeons in training as well as attending staff surgeons. Excluded are all patients with primary carcinoma of the distal esophagus, other malignant gastric neoplasms, all patients not operated on, and all patients whose operations were either diagnostic or palliative. Two hundred forty-two patients underwent resection for cure, and only 4 were lost to followup, a 98% followup rate. One hundred ninety-five patients were followed for 10 years. In all cases the pathologic findings were reviewed. On the basis of the gross description of the freshly resected specimen, cases were grouped as "small malignant ulcer" or "other adenocarcinoma." A "small malignant ulcer" was defined as being less than 4 cm in diameter with no associated mass effect. Ulcers larger than 4 cm, ulcers with associated tumor mass, ulcerating tumors, exophytic lesions, linitis plastica, and superficial spreading carcinoma were all grouped as "other adenocarcinoma."

Duration of preoperative symptoms was obtained from clinical records. Symptoms included weight loss, persistent pain or epigastric distress, anorexia, dysphagia, and gastrointestinal hemorrhage.

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TABLE 1. *Adenocarcinoma of the Stomach—Long-term Survival*

Followup	No. Patients	% Survival
5 Yrs	45/242	18.6%
10 Yrs	17/195	7.1%

Operative mortality figures reflect all deaths within 30 days of operation. Percentages for long-term survival rates represent the number of survivors divided by the total number of patients in the study. The 4 patients lost to followup were presumed dead of carcinoma of the stomach.

Using the original operative records, we classified surgical procedures into three groups: "distal subtotal gastrectomy," "proximal subtotal esophagogastrectomy," and "total gastrectomy." In no case was a malignant tumor resected for surgical cure by wedge excision alone. The "distal subtotal gastrectomy" group consisted of those patients undergoing distal gastrectomy with resection of the gastroduodenal and gastrophrenic omenta, with or without resection of the spleen, transverse colon or pancreatic tail. In some cases only a rim of proximal stomach remained. The "proximal subtotal esophagogastrectomy" group included resection of distal esophagus, proximal stomach, spleen, and gastrophrenic omentum, with or without partial pancreatectomy. "Total gastrectomy" included resection of the entire stomach, the esophagogastric junction, spleen, gastrophrenic and gastroduodenal omenta, with or without partial pancreatectomy or transverse colectomy. Thoracic or thoraco-abdominal incisions were often used in these latter two groups.

Results

Table 1 shows overall survival data. Forty-five (18.6%) of the 242 patients survived 5 years. Seventeen (7.1%) of 195 patients resected prior to January 1, 1964 survived 10 years. The 26 patients with "malignant gastric ulcer," however, experienced a 5-year survival of 53.8%, more than three times higher than the "other adenocarcinoma" group (14.4% 5-YSR). At 10 years the difference between these two groups, 15.0% 10-YSR and 8.0% 10-YSR respectively, was less pronounced (Table 2).

The majority of patients (73%) had a "subtotal distal gastrectomy" with an operative mortality rate of 4.5%.

TABLE 2. *Factors Influencing Survival: Nature of Primary Lesions*

	Malignant Gastric Ulcer (<4 cm)	Other Adenocarcinoma
Survivors/Total		
at 5 yrs	14/26	31/216
at 10 yrs	3/20	14/175
% Survival		
at 5 yrs	53.8%	14.4%
at 10 yrs	15.0%	8.0%

TABLE 3. *Surgical Treatment & 30-Day Operative Mortality*

Operative Procedure	Operative Deaths	% Mortality
Distal Subtotal Gastrectomy	8/177	4.5%
Proximal Subtotal Esophagogastrectomy	7/54	12.9%
Total Gastrectomy	2/11	18.2%
Totals	17/242	7.1%

The "malignant gastric ulcer" sub-group, all of whom had this operation, had no operative deaths. The operative mortality was 12.9% for "subtotal proximal esophagogastrectomy" and 18.2% for "total gastrectomy." Summary figures show a total of 17 deaths for an overall operative mortality rate of 7.1% (Table 3). Correlating 5-year survival with the type of operation, we found that "distal subtotal gastrectomy," "proximal subtotal esophagogastrectomy," and "total gastrectomy" resulted in 20.3%, 14.8%, and 9.1% respective 5-year survival (Table 4).

Looking further at 5-year survival we found that 13 (28.9%) of the 45 five-year survivors had histologically verified spread of cancer into lymph nodes. Taking the 158 patients with positive lymph node involvement as a group, we found a 5-year survival rate of 8.2%. Conversely, 32 (71.1%) of the 45 five-year survivors had negative lymph nodes. However, the total sub-group of patients (84) with negative lymph nodes experienced a 5-year survival rate of only 38.1% (Table 5).

Also of note is that 15.5% of 5-year survivors had histologically verified presence of tumor cells in the distal or proximal margin of resection. This condition was also found in 29.5% of non-survivors (Table 6).

Relating survival to the duration of preoperative symptoms revealed that 5-year survivors had a longer average symptomatic pre-operative interval (16.9 mo.) than did non-survivors (11.0 mon.). This observation held for both the "other adenocarcinoma" and the "ulcer" groups (Table 7). Further evaluation indicated that for the series as a whole, the longer the symptomatic preoperative period, the higher the 5-year survival. Specifically, 29 of 174 patients with symptoms for less than 6 months (3.0 mon. avg.) survived 5 years (16.9% 5-YSR), and 16 of 68 patients with symptoms longer than 6

TABLE 4. *Factors Influencing Survival: Type of Operation*

Operation	5-Yr Survivors	% Survivors
Distal Subtotal Gastrectomy	36/177	20.3%
Proximal Subtotal Esophagogastrectomy	8/54	14.8%
Total Gastrectomy	1/11	9.1%

TABLE 5. Factors Influencing Survival: Cancer in Regional Lymph Nodes

	Entire Series	5-Yr Survivors	% Survival
Total No. Patients	242	45	18.6%
Patients with Negative Nodes	84	32	38.1%
Patients with Positive Nodes	158	13	8.2%

months (27.6 mon. avg.) survived 5 years (23.6% 5-YSR). Within the group complaining of symptoms for longer than 6 months, 30 patients related symptomatic periods exceeding 24 months (60.0 mon. avg.). Nine of these 30 patients survived 5 years (30.0% 5-YSR) (Table 8). Interestingly, 4 of these 9 surviving patients with extended periods of symptoms had small malignant gastric ulcers (Table 9), and all 4 had been treated for years with medical therapy. Fortunately for these patients, the chronicity of their disease finally resulted in operation.

Discussion

In the United States, cancer of the stomach has fallen from the number one cause of cancer death to 24th over the past 40 years.¹ In previous decades, rates as high as 10%³ or 11%⁶ were reported for the incidence of malignancy in benign-appearing gastric ulcers. More recently Thio and White⁷ have documented the low rate of malignancy (3.3%) in their followup series of 363 patients whose initial diagnosis was benign gastric ulcer. Against this background of decreasing incidence of gastric malignancy, it is not surprising to find that proponents of a protracted medical approach to the patient with a benign-appearing gastric ulcer have grown bolder. Over one-third of the present series of patients had symptomatic preoperative periods exceeding 6 months. Consistent with the earlier suggestion of Ochsner, Blalock and McPherson,⁵ we found that, within our series of patients, prolonged symptomatic preoperative periods correlated positively with increased 5-year survival. In addition, it is of note that in 28.9% of 5-year survivors the disease had spread into regional nodes. These observations might lead one to conclude that survivors had minimally invasive, slow-growing tumors. However, of the 9 survivors whose symptomatic period exceeded 24 months (62.0 mon. avg.), 4 fell into the "malignant gastric ulcer"

TABLE 6. Factors Influencing Survival: Cancer at Proximal or Distal Line of Resection

	No. with Positive Margin	Total No.	%
Entire Series	66	242	27.3%
5-Yr Survivors	7	45	15.5%
Non-survivors	59	197	29.5%

TABLE 7. Factors Influencing Survival: Duration of Symptoms

Patient Groups	Average Duration of Symptoms Prior to Surgery (mo.)
45 5-Year Survivors	16.9
31 "Mass"	15.4
14 "Ulcer"	20.6
197 Non-survivors	11.0
185 "Mass"	10.7
12 "Ulcer"	11.7

group. These 4 patients all had several years of treatment for gastric ulcer, and all were operated on for chronicity of symptoms. If these 4 cancers were present from the beginning, they were exceedingly slow-growing indeed. Here Ravdin and Horn's thesis⁶ that chronic gastric ulcers may undergo malignant change might hold true. However, it would apply to a fairly small number of patients. The majority of patients with gastric cancer shows rapid progression of symptoms leading to an operation that is performed too late. The physician on the front line must be increasingly astute in assessing abdominal complaints to diagnose the gastric cancer patient early enough to effect cure. If the patient with epigastric complaints also admits anorexia, then extensive diagnostic work-up, including gastric analysis, radiological examination, gastroscopy, peroral biopsy, and cytology, should proceed at once,^{3,5} even before a trial of medical therapy.

Recent reports indicate that, of all patients with gastric malignancy, only 32%⁴ to 46%² are resectable for cure. Within this group, patients with small malignant ulcers enjoy enhanced survival. That these lesions may represent malignant change in areas of previously benign ulceration is strongly suggested by selected case histories. Since our experience indicates that operative mortality in this group is extremely low, we encourage an aggressive operative approach to the patient with a benign-appearing, small gastric ulcer that does not respond promptly and completely to intensive medical therapy. The operation chosen should provide wide excision, even for small lesions. The proximal line of resection should be 3.0 to 5.0 cm above the ulcer. Regional lymph nodes contained in the gastrohepatic and gastrocolic omenta should routinely be removed by *en bloc* resection, regardless of a frozen section diagnosis of benign gastric ulcer. If permanent sections report a malignant diagnosis no further surgery need be done. The continued decline

TABLE 8. Relation of Duration of Symptoms to Survival

Duration of Symptoms (mo.)	Number of Patients Total	Survivors	5-Yr Survival %
< 6 (3.0 avg.)	174	29	16.9%
> 6 (27.6 avg.)	68	16	23.6%
>24 (60.0 avg.)	30	9	30.0%

TABLE 9. *Factors Influencing Survival: Symptomatic Period Exceeding 24 Months*

Patient Groups	Average Duration of Symptoms Prior to Surgery (mo.)
Survivors	
5 Mass	64.0
4 Ulcer	60.0
Non-Survivors	
20 Mass	57.3
1 Ulcer	72.0

in survival during the second 5-year postoperative period may indicate inadequate resection of lesions that are biologically less aggressively invasive. Finally, our experience indicates that, in selected patients with extensive lesions, total gastrectomy can be done with an ac-

DISCUSSION

DR. R. B. WELBOURN (London, England): Cancer of the stomach remains a common disease and the over-all prognosis is still very bad. Happily the incidence is falling here and in the United Kingdom, but our incidence is still 30-34 per 100,000 of the population, which is about two times that in the U.S.A.

Dr. White's figures are very interesting and very good, but I wonder what proportion of the total patients with gastric cancer they represent. Operability and resectability rates vary greatly. In a recent prospective multicenter cooperative survey in Europe, under the auspices of the International Federation of Surgical Colleges, in which we took part, the operability rate was 92% and the resectability rate 52%. If Dr. White's figures are similar, all his survival data must be divided by two to give the over-all picture for gastric cancer.

This experience is similar to that of others, namely that two groups of patients do well. The first are those with small lesions, which are presumably early. This finding underlines the importance of screening and early diagnosis in countries like Japan, where the disease is very common and increasing in frequency. The second group are those with a long history, in whom presumably the body resists the growth actively. Immunological studies in these patients might be rewarding.

I am not impressed by the ulcer-cancer hypothesis, because several large series of benign gastric ulcers have now been followed for several years without any of them becoming malignant. I think that gastric cancers are malignant from the outset.

At Hammersmith Hospital we have been particularly interested in the palliative treatment of the incurable disease with fast neutrons, provided by the Medical Research Council's cyclotron. This aspect of gastric cancer is not strictly within the terms of reference of the paper, but you may be interested in our findings. The work is being done by Dr. Mary Catterall and her colleagues, and the surgeon involved is John Spencer. Thirty-nine patients have been treated, 30 with inoperable tumors, 3 with residual tumor and 6 with local recurrence. All lesions were verified histologically. The ages ranged from 32 to 82 years. Neutrons were delivered at 7.5 MeV, and a dose of 1440 rads was given to the tumor area in 32 patients. In 7, smaller doses were given for various reasons. The beams are of comparatively low energy and have poor penetration, and for the treatment of gastric cancer they are only suitable for thin patients.

The mean survival was 5 months and the longest survival was 2 years. Most patients died from metastases. (slide) This shows the relief of symptoms and signs in the 32 patients in whom treatment was complete. Severe bleeding was relieved in all of the six patients for whom the treatment was given. Vomiting, pain, and a palpable mass were relieved in over 80% of the patients; and then dysphagia, anorexia, and loss of weight in rather smaller proportions.

Relief of vomiting and anorexia was particularly gratifying because these are the very symptoms which conventional radiotherapy often causes.

All the lesions were followed radiographically. The stomachs shrunk

ceptable mortality rate and definite chance of long-term survival.

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in size, motility diminished progressively, and the mucosal patterns became increasingly abnormal.

Five patients required surgical operations, for intestinal obstruction due to tumor in 3, for recurrence of gastric bleeding in 1 and for removal of an esophageal tube in 1. No palpable tumor was found in the irradiated area in any and the incisions, including anastomoses, healed well in 4 of the patients.

Autopsies were performed in 14 patients. There was no palpable tumor in the irradiated area in 10. In 4 tumor was present macroscopically, 3 had had partial treatment only. Histological examination showed proliferation of connective tissue and considerable fibrosis. There were a few inactive-looking tumor cells buried in fibrous tissue, and vascular changes were marked.

Neutron therapy clearly has a useful place in the palliative treatment of advanced gastric cancer. We wonder whether it may have a curative role, combined with operation and/or chemotherapy, in earlier cases, especially when beams of higher energy and penetration become available for clinical use.

DR. FREDERICK H. BOWEN (Jacksonville, Florida): I rise to present a long-term survival of a patient with multiple organ resection for gastric carcinoma. I'm sorry I only have one case.

In July, 1956, I saw a 52-year-old white woman who was complaining of generalized burning over her abdomen of one to two years' duration. She felt that this burning was more intense in the region of the umbilicus. It was made worse by drinking Coca Cola, and was relieved by drinking milk. The burning was worse when she was worried or tense. The patient said that she had furriness of her tongue, and complained that she had a cotton-like taste in her mouth.

Sigmoidoscopic examination revealed a posterior anal fissure. The patient's hemoglobin was 9 gm. An upper g.i. series revealed a long, low J-shaped stomach with the greater curvature well down in the pelvis. I don't know why this g.i. series didn't show the carcinoma. I saw the films, and I couldn't see it. Neither could the radiologist.

The patient was started on iron, and on the 22nd of September the epigastric burning was less, and her hemoglobin had risen to 10.5 gm.

Four months after I first saw the patient she experienced severe pain to the left of the umbilicus, and on examination a tender, two-inch diameter mass was noted in that region. The pain increased, and the patient began to have nausea following her evening meal. A negative IVP and barium enema were done. This barium enema showed slight narrowing in the center of the transverse colon.

At operation a ragged ulcer measuring 7 x 4 cm in size was noted along the greater curvature of the stomach, extending down to the pylorus. The tumor was adherent to the anterior abdominal wall, just inferior to and just to the left of the umbilicus. The tumor extended into the transverse mesocolon and into the transverse colon microscopically, but the mucosa was not involved.

An 80% Billroth II gastric resection was done, a resection of the anterior abdominal wall was done, and also 20 cm of the transverse colon was resected. A 14 French catheter was inserted into the trans-

verse colon four inches proximal to the suture line, and 1% neomycin solution was inserted into the transverse colon during and after operation.

The patient has survived for 18 years following this extended operation for the tumor, which was reported as an anaplastic, poorly differentiated adenocarcinoma of the stomach.

At the suggestion of Dr. Coley Johnston, I had my pathologist get out the slides on this case and review them. He states that, in his opinion, this is a carcinoid of the stomach, but he will make further sections and send the slides around to other pathologists for opinions.

I want to apologize to Dr. Fitts and the Association for presenting this case in the discussion of a paper on adenocarcinoma. At the time I presented the case I felt it was a case of adenocarcinoma.

DR. WILLIAM H. REMINE (Rochester, Minnesota): Because of the decrease in incidence, I think our attention has been drawn away from the subject of carcinoma of the stomach. It's a subject I have been interested in for a number of years, first stimulated by Dr. Walters, who is here today, and also by Dr. Priestley, who is a member of this Association.

Because of a question that was directed to me, I decided to study long-term survivors. The question was: Do you ever really cure anybody with carcinoma of the stomach? And feeling very definitely that we do, I went back to our files and pulled all of the cases that had lived 10 years or longer from 1907 to 1955. A number of these had been operated on by Dr. Walters, as a matter of fact. I think this would be of interest to you, because we used all the yardsticks that we usually use to measure curability for carcinoma of the stomach, such as location of the lesion, the type of operation, gastric acids, hemoglobin, duration of symptoms, and lymph node involvement.

There were 4586 patients who were operated on during that period of time with hope of cure, and of those there were 1067 who lived 10-56 years. We discarded all of the lymphosarcomas and leiomyosarcomas, and ended up with 957 who had adenocarcinomas; I thought we'd take just the very worst ones.

This was very interesting, because something happened after five years. We use these yardsticks to measure longevity up to five years, but after that they don't seem to apply. I'd like to give you the figures to bear this out.

Sixty-eight of these had a preoperable, palpable mass; 12 had multiple lesions; one had three lesions in the stomach. So this doesn't seem to affect total longevity; that is, it doesn't mean that all of them can't be cured.

The lesions were found in all parts of the stomach, the majority in the lower half, but 11 involved the entire stomach, and 52 were larger than 10 cm. So size didn't seem to make a great deal of difference here.

The type of operation: 285 had half of the stomach removed, 505 had three quarters of the stomach removed, 17 had total gastrectomy, and there were 150 that weren't stated in the early years.

The gastric acids: 434 had free acid, 375 were achlorhydric and 148 weren't stated.

Hemoglobin: 653 had normal hemoglobin, 222 were anemic, and 82 were not stated.

The duration of symptoms (which was mentioned in this talk): 497 had symptoms one year or longer, 433 had symptoms less than one year; 17 were not stated.

The microscopic grade of the lesion: 480, or roughly half of them, had grades 3 or 4. It's been stated in the literature that most of your cures will come in the lower grades; that is, 1's and 2's. And you only have 15% of them that turn out to be 1's and 2's, so that limits your possibility of cure. But half of these were 3's and 4's.

Extension of the lesion: serosal invasion was present in 380 of the specimens that we examined, liver extension in three, pancreatic extension in two.

Lymph node involvement was interesting, because there were 281 that had nodes involved, and 676 had no nodal involvement. Only six of these had subpyloric nodes involved.

At the end of the study there were 356 patients alive and well. One had lived 56 years.

DR. JULIAN K. QUATTLEBAUM (Savannah, Georgia): I rise to recall a discussion by Dr. J. M. T. Finney, Jr. before this Association some years ago. Dr. Finney, Jr., in discussing a paper on cancer of the

stomach, mentioned that he had received an inquiry from a doctor in North Carolina who had treated a patient for some type of terminal disease, probably leukemia, and had written him to confirm a statement the patient had made that Dr. J. M. T. Finney, Sr., some 30 years earlier had operated on him for cancer of the stomach. Dr. Finney had informed the patient that he had been unable to remove two very firm nodes high up under the diaphragm he felt sure were invaded by carcinoma. Dr. Finney, Jr. was asked to confirm this by reviewing the operative notes made by his father. This he did. Some time later the patient died, an autopsy was performed, which disclosed the two nodes containing cancer high under the diaphragm, just as had been described by Dr. Finney, Sr.

This also confirms the statement found in a book by Eusterman and Balfour that a patient with cancer of the stomach may be cured even if all involved lymph nodes are not removed; and that there is evidence that cancer in any situation, removal of the primary growth and of the immediately adjacent lymphatic structures may bring about permanent cure, even if involved lymph nodes are left; the remaining nodes in such cases act as a barrier to further dissemination of the disease. I think one should bear this in mind in operating upon such malignancies and not be tempted to do an ultraradical operation, which might jeopardize the life of the patient when removal of the primary growth and related nodes might be equally effective in arresting the disease.

Again I wish to say that this discussion is largely to recall the memory of two great Finneys, J. M. T., Sr. and J. M. T., Jr., who were so prominent in affairs of the Southern Surgical Association over the years.

DR. RALEIGH R. WHITE IV (Closing discussion): Just taking the discussants in order, Professor Welbourn, we have found not through our direct experience, but through looking at the recent literature, that the resectability rate seems to run around 32%, as represented in a very large recent Scandinavian national series, to 46% from a large clinic series in the last year in this country.

The question of the palliative treatment for the incurable patient certainly is a very important issue. It really involves a great majority of the patients with this disease. I think the fast-neutron therapy will probably be widely applied in the future. We certainly appreciate your information in that regard.

Dr. Bowen, I think that our experience, and also the case referred to by Dr. Quattlebaum, would be supportive of your idea about the difficulty in predicting survival in any specific patient. In reviewing our cases, we found the traditional guideposts that we use to evaluate the extent of disease helpful in predicting which patients would not survive, but it was very hard to predict which patients would survive. In fact, very similarly to Dr. ReMine's experience, about a quarter of our survivors had positive lymph nodes at the time of their original operation, and several of our long-term survivors were people with massive tumors. In fact, almost a quarter of our 5-year survivors had tumors that were not totally resected, as evidenced by positivity of the margins of resection on the histologic evaluation of the resected specimen. Yet these people were five-year survivors.

In that regard, we thought it was interesting that the over-all survivorship continued to decline over the second five-year interval, and as you saw, even for the small malignant ulcer group, the survival rates at ten years were half what they were at five years. And quite a few of these people, although living at five years, were noted in their records to be living with the presence of known recurrence or spread of their disease.

I think that some of these patients indeed represent situations where their immune responsiveness is controlling the tumor. And in the case that Dr. Quattlebaum presented, it seems that that patient likewise was in a similar situation.

I would just like to emphasize one final point. It was surprising to us to find how many of these patients really had quite prolonged periods of medical therapy prior to their surgery. This at least seems true in Philadelphia. Perhaps it might be true in your home communities as well.

In closing, I wish to express the gratitude of a young man to the Southern Surgical Association—and to Dr. Fitts—for the privilege of closing this discussion. For reasons known to many of you, this moment provides a special thrill for me, and a personal satisfaction that I will long cherish.

Chemotherapy as an Adjuvant to Surgery for Colorectal Cancer

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A combined intraoperative and postoperative adjuvant program of 5 - Fluorouracil (5 FU) for patients undergoing "curative" resection for adenocarcinoma of the colon and rectum was initiated as a randomized clinical trial in January 1968. Patients at the Medical College of Virginia and the University of Virginia were randomly assigned to an intraluminal 5 FU or intraluminal control (Saline) group and were so treated at the time of surgical resection if findings at operation indicated that all gross neoplastic disease could be resected. Patients with operative findings denoting incurability were eliminated from the study after surgical exploration. Those patients receiving intraluminal 5 FU (30mg/kg) received intravenous 5 FU (10mg/kg) on each of the two first postoperative days and 5 subsequent postoperative courses of oral 5FU (90 mg/kg in each 18 day course) over a one year period. By December 31, 1973 (6 years) 156 patients undergoing "curative" resection were entered into the study. Survival curves and "disease free" curves for comparison of the group receiving adjuvant 5 FU therapy with the control or "No Treat" group reveal no significant benefit from this intensive adjuvant course of 5 FU thus far. Continued assessment of these patient groups and their subgroups will be required to develop confidence in these findings but the data thus far suggest no potential benefit from this particular adjuvant program.

THE RATIONALE for combining chemotherapeutic agents with curative operative attempts for "solid tumors" has had great appeal as a potential means of improving end results of surgery for cancer. Despite a great deal of interest in this approach there have not yet been any clinical studies conclusively demonstrating benefit from surgical adjuvant chemotherapy for any of our common adult cancers. In January 1968 we initiated a cooperative two institution clinical trial designed to

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evaluate a combined intraoperative and long term postoperative adjuvant 5 fluorouracil program for cancer of the colon and rectum. This is a preliminary report of our findings

The surgical adjuvant studies for large bowel cancer reported thus far include trials of thiotepa,⁷ 5 fluorouracil (5 FU),^{6,8} and flurodeoxyridine (FUDR).³ These trials have used either intraoperative chemotherapy,^{4,8} chemotherapy immediately following the surgical resection,⁶ or limited additional courses of chemotherapy later in the postoperative period.^{3,6} Some studies have included only patients undergoing "curative" resection, while others have included separately identified groups undergoing palliative resection as well. The results have been well summarized by Carter and Friedman.²

The first major cooperative clinical trial for large bowel cancer, reported by Holden et al.,⁷ was carried out with two different dosage levels of thiotepa due to increasing morbidity associated with the initial drug dosage chosen. Adjuvant therapy with this agent was limited to the immediate post-operative period. Later evaluation of this trial did show a trend toward benefit from adjuvant chemotherapy with thiotepa in the subgroup of females over 55 years of age who received the initial higher dosage schedule. Unfortunately this beneficial effect was balanced by the higher morbidity experienced at this high dose rate. The overall case for adjuvant therapy with alkylating agents was not made in this particular study, but this was only an immediate postoperative program with no effort to accomplish chronic treatment of minimal residual disease.

Interest then shifted to the fluorinated pyrimidines as

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possible adjuvants due to the demonstrated effectiveness of 5 fluorouracil in the management of advanced carcinoma of the colon and rectum. Rousselot and co-workers⁸ initiated a trial of intraluminal 5 FU with immediate postoperative intravenous 5FU administration in a series of patients with cancer of the colon and rectum. There appeared to be a favorable trend in long term survival with adjuvant 5FU in comparison to prior surgical results, particularly with those patients who demonstrated lymph node metastasis. On this basis a multi-hospital cooperative project with double blind randomization of patients undergoing "curative" resection was initiated and this study is still in progress.⁴ Meanwhile, two controlled trials, carried out by the Veterans Administration Surgical Adjuvant Cancer Chemotherapy Group, studied patients with carcinoma of the large bowel to determine the possible benefits of 5 FU⁵ and of FUDR³ as adjuvants to surgical resection. In both of these trials after "curative" resection, patients were given adjuvant therapy soon after surgery and again approximately 6 weeks following surgery. In neither of these studies could benefit from the adjuvant be demonstrated. In a more recent long range trial of intermittent postoperative systemic 5 FU by this Veterans Administration Surgical Adjuvant Group, there has been no evidence of survival benefit with intermittent courses carried out to the 19th month following operation. The followup period for this latter study is still quite short (2 years) and final conclusions cannot be drawn. However, it is fair to say that none of the adjuvant drug trials performed thus far have demonstrated convincing benefits from the adjuvant chemotherapy approach to surgery for colon and rectal cancer.

The rationale of this current study was based on the concept that intraluminal and intravenous chemotherapy at the time of operation might add some benefit (as suggested by the data of Rousselot et al.⁸) but long term postoperative administration of the chemotherapeutic agent might have supplementary benefit as well. Clinical trials prior to this study have been limited to relatively short term courses of therapy and it was conceivable that a useful margin of benefit could be detected by a more aggressive approach than had been employed up to the time this study was initiated. It was also considered worthwhile to give a maximum trial of 5 FU as the adjuvant since this agent had been shown to have a definite, albeit low, order of activity against measurable disease in patients with large bowel cancer (15-25% objective response rates).

Description of Study

This prospective surgical adjuvant study was initiated in January 1968 and the results to be reported include those patients entered January 1, 1968 through December 31, 1973 from the surgical services of the Medical College

of Virginia Hospitals (Richmond) or the University of Virginia Hospital (Charlottesville). The random assignment of eligible patients with colon and rectal cancer to either a control or a 5 FU adjuvant group had been made prior to operation by calling a central point at each of the two institutions. Separate lists of random numbers for this purpose are maintained for cancer of the rectum (<15 cm from the anal verge) and cancers of the colon (>15 cm from the anal verge). Essentially equal groups of colon and rectal lesions are assigned to each group by this means.

Patient Eligibility. All patients with a clinical diagnosis of colon or rectal cancer and preoperative findings compatible with "curative" resection are eligible for this study except: 1). Patients considered "inoperable" for medical reasons or unsuitable for standard surgical resection for the same reasons; 2). Patients that have received prior irradiation, chemotherapy, or surgical resection for the current cancer other than preliminary colostomy for obstruction; 3). Patients with a primary cancer of another site (other than basal or squamous cell carcinoma of the skin); 4). Patients who are pregnant at the time of diagnosis; 5). Patients more than 80 years of age; 6). Patients who will require multiple organ resection, such as pelvic exenteration, due to extracolonic involvement of other organs (this observation may not be made until time of operation); 7). Patients with carcinoma of the colon who have free perforation of the cancer itself or the more proximal colon; 8). Patients who have a preoperative white blood cell count less than 4,000, or preoperative platelet count less than 150,000.

The fact that patient entry into this protocol occurred prior to the time the operative procedure was actually accomplished led to a need for a system to eliminate patients found to be ineligible for a curative surgical procedure on the basis of operative findings. Some patients initially entered into the study were subsequently eliminated at the time of exploration if operative findings revealed factors that made the patient ineligible for the study as designed. These operative factors were either the presence of metastases, the direct involvement of extracolonic organs by the cancer itself, or the unexpected finding that the clinical diagnosis of colorectal cancer was incorrect. The preoperative assignment of patients to the 5 FU treatment or control groups prior to final pathologic classification also led to our inability to stratify the patients on the basis of various prognostic factors that may be found on pathologic study.

Intraoperative and Early Postoperative Management. After exploration to determine the presence or absence of metastases or extra colonic involvement by the neoplasm, the presence of the cancer is confirmed by gross examination. Early in the operation umbilical tapes are placed inside the proposed lines of resection and are so placed that they include the marginal vessels adjacent to

the bowel. For rectal lesions a purse string suture is placed around the anus prior to the exploratory surgery and only one tape is placed around the bowel on the proximal side.

After the bowel segment is isolated, 5 FU (30 mg/kg) diluted in 50 ml of physiologic saline, or 50 ml of saline without agent, is injected into the bowel lumen and the needle puncture site closed with a purse string suture. Although dissection for colectomy is begun, the blood supply to the colon is not ligated for a period of 30 minutes after intraluminal instillation. A standard radical colectomy is then performed using a "no touch" technique in so far as this is possible for the site of the particular primary lesion. This consists of a right hemicolectomy, left hemicolectomy, or abdominoperineal resection with the associated mesentery and blood vessels. For rectal lesions the operation includes ligation of the inferior mesenteric artery either at the aorta or just distal to the left colic branch of the inferior mesenteric artery.

On the first and second postoperative days patients randomized for adjuvant 5 FU receive intravenous 5 FU (10 mg/kg) in one liter of intravenous physiologic saline each day. All other details of postoperative management are standard and the same for both the control and the 5 FU treated patients. The overall procedure followed in the operative and immediate postoperative period is essentially the same as that described by Grossi, Nealon, and Rousselot.⁴ The procedural addition in this study is the long term postoperative course of 5 FU.

Pathology Evaluation. Pathologic study has confirmed the diagnosis of adenocarcinoma in all patients remaining in the study and pathologic staging has been carried out at both institutions. A final pathologic diagnosis of a benign neoplasm or a malignant neoplasm other than adenocarcinoma has been a reason for elimination of the patient from the study. Microscopic proof of invasion of extracolonic organs has also been a reason for elimination of a patient from the study.

Postoperative Adjuvant Chemotherapy. Patients in the 5 FU treatment group receive 5 postoperative oral courses of 5 FU with the initial course being 30 days postoperative. Additional courses are begun each two months for a total of 5 complete 18-day courses. Oral 5 FU medication in fruit juice is administered each morning of treatment giving 12 mg/kg daily for 4 days and 6 mg/kg every other day for 7 doses (or less if leukopenia, thrombocytopenia, or signs of oral or gastrointestinal toxicity develop). Patient status and hematologic studies are monitored prior to each course of chemotherapy and at weekly intervals during these courses. Modification of drug dosage is dependent on both the clinical status and laboratory studies.

During the postoperative courses of treatment with 5 FU the drug is discontinued if the white blood cell count is less than 4,000 or the platelet count is less than 90,000.

One half the dose outlined is given on the same schedule if the white blood cell count is between 4,000 and 5,000 or the platelet count between 90,000 and 125,000. Also if diarrhea develops, the drug is discontinued, but if the significance of this finding is questionable, and later followup substantiates the lack of toxicity, the drug is restarted.

Followup Observations. Patients on this study are followed monthly during the first year, every two months the second year, every 3 months the third year, and every 4 months the fourth and fifth years after surgery. Patients are subsequently followed every 6 months after the 5 year interval. Special forms outlining the patient's status are filled out at the time of each evaluation and these include details of the complete physical examination, protoscopic examinations at intervals to search for local recurrence or metastasis, and intermittent biochemical and x-ray evaluations. Patients in both the 5 FU adjuvant and control groups are followed at the same intervals. No placebo is used for patients in the control group as this study has not been performed in a "double blind" fashion.

Results

Of the 241 patients entered into this study by preoperative randomization January 1, 1968 through December 31, 1973, 85 patients have been eliminated following randomization. Two of these patients refused to participate in the study after initial randomization and 83 patients were subsequently found to be ineligible due primarily to findings at the time of operation or on later pathologic study (Table 1). The total number of patients eligible for analysis after this operation and pathologic evaluation is 156 patients (123 from Medical College of Virginia Hospitals and 33 from the University of Virginia Hospital). Of this total group 80 were randomized into the 5 FU adjuvant treatment group and 76 into the control group.

The patient profiles of the control and adjuvant therapy groups are shown in Table 2. The number of rectal cancer and colon cancer patients in each group are essentially equal in view of the stratification of patients into these categories at the time of randomization. The proportion of patients in each group with histologically involved

TABLE 1. Reasons for Ineligibility for Clinical Trial After Initial Preoperative Randomization.

Total patients entered-	241
Subsequent ineligibility:	
Intra-abdominal metastases	46
Lesion not cancer	18
Other malignant colon neoplasms	2
Invasion extracolonic organs	9
Multiple colorectal cancers	1
Refused surgery after entry	2
Other procedural problems	7
Total	85
Eligible patients retained in trial	156

TABLE 2. Patient Profiles of Eligible Patients in the Control and 5 FU Groups (Clinical Trial of Adjuvant Chemotherapy After "Curative" Resection for Colorectal Cancer).

	Adjuvant 5 FU	Control
Total cases	80	76
Sex (M:F)	40:40	36:40
Age—Mean	60.7	63.4
Range	33-80	24-85
Anatomic site		
Colon (> 15 cm)	49	49
Rectum (< 15 cm)	31	27
Pathologic stage		
Dukes' A or B	53	48
Dukes' C	27	28
Total cases	80	76

lymph nodes (Dukes' C) are quite comparable by virtue of the randomization process although this pathologic finding was unknown to the investigator at the time of the patient's entry into the protocol. Age and sex, other factors that might affect the subsequent treatment results, are also essentially similar in the two groups. The operative complication rates and mortalities are also similar for the control and adjuvant therapy groups (Table 3).

Drug Dosage Received. There have been no signs of hematologic or other toxicity in the early postoperative period in the adjuvant treatment group. The number of complete courses of chemotherapy and the total drug dose received in the first postoperative year is shown in Tables 4 and 5. In most instances incomplete drug dosage and incomplete numbers of postoperative courses were due to leukopenia, using the criteria for hematologic toxicity previously defined. Twenty-two patients in the 5 FU adjuvant group developed some degree of leukopenia and 8 patients developed signs of gastrointestinal toxicity which led to dosage reduction or discontinuation of 5 FU. The toxicity observed was evenly distributed between the colon and rectal groups (Table 6).

The total planned course of 5 FU has been successfully accomplished in 67% of the patients in the adjuvant therapy group. This, plus the fact that 23% of the adjuvant treatment group have received less than 40% of the total planned dosage, due primarily to hematologic toxicity, suggests that the dosage schedule chosen is in an

TABLE 3. Operative Complications and Mortality in Clinical Trial of Adjuvant 5 FU After "Curative" Resection for Colorectal Cancer

	Total Patients	5 FU Group	Control Group
Number	156	80	76
Post-op Complications	38 (24%)	20 (25%)	18 (24%)
Operative Mortality (<30 Days)	3 (1.9%)	2 (2.5%)	1 (1.3%)

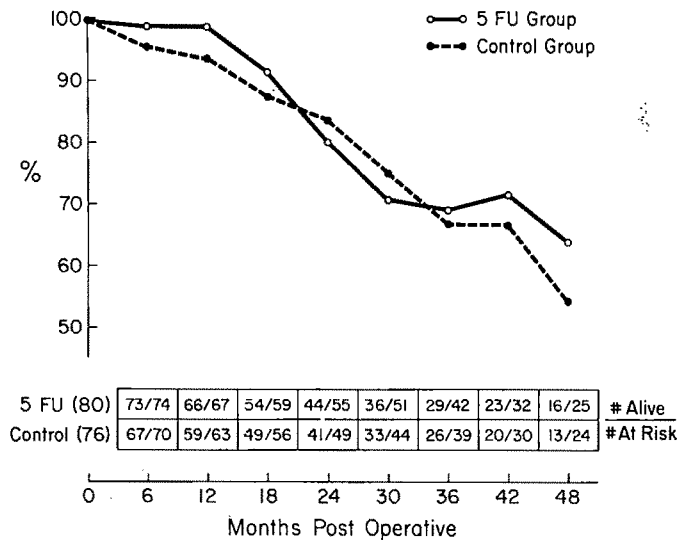


FIG. 1. Colorectal cancer. Survival after "curative" resection (all stages).

effective range for the purpose of this study. Following the conservative guidelines outlined for dose restriction there have been no significant sequelae from chemotherapeutic treatment in the adjuvant group. Oral ulceration was not seen as a concomitant of 5 FU toxicity.

Survival Statistics. The results in the combined rectal and colon control and 5 FU adjuvant therapy groups thus far can be estimated from survival curves that have been constructed for each of these groups. The data shown at each 6 month interval after operation are based on the time "at risk" for each patient at the time of the survival calculation for this report (May 1, 1974). The three patients who died as a result of the operation are eliminated from this calculation. Also, those patients who clearly died from other causes, without evidence of recurrent or

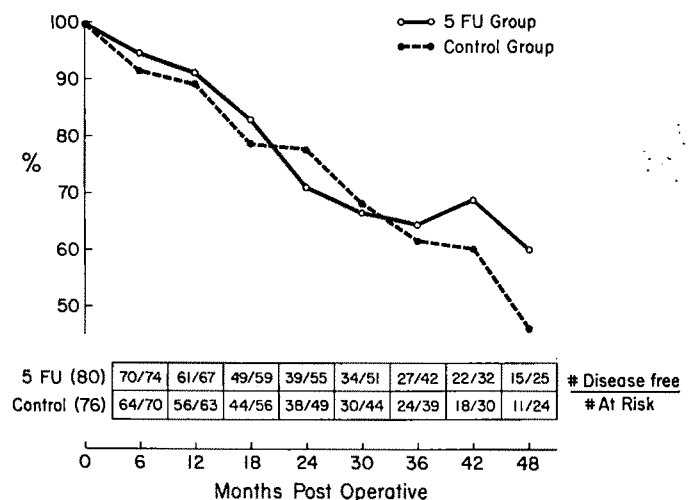


FIG. 2. Colorectal cancer. Survival free of recurrence after "curative" resection (all stages).

TABLE 4. Total Courses of Oral 5 FU Received in Adjuvant Chemotherapy Group in First Postoperative Year of Clinical Trial*

No. of Postop Courses	Total Group	Colon Cancer	Rectal Cancer	Colon & Rectal Cancer	
				Dukes' A & B	Dukes' C
All 5 Courses	50/75 (67%)	29/46 (63%)	21/29 (72%)	34/50 (68%)	16/25 (64%)
< 2 Courses	17/75 (23%)	11/46 (24%)	6/29 (21%)	12/50 (24%)	5/25 (20%)

* 75 patients >1 year postop

metastatic cancer, were considered free of cancer at the calculated 6 month interval prior to death, but were eliminated from the calculation in the next period "at risk." The actual data and the visual graph of these results reveals no detectable difference in survival between the two groups (Fig. 1). The 95% confidence limit at three years indicates that, on the basis of current figures, the survival rate for the 5 FU group will not exceed the control group by more than 19%. Looking at the data for three year survival in another way, the probability of finding a statistically significant difference ($P < .05$) is 0.7 if there was a 20% difference actually present. Longer followup observations on patients already entered into this protocol will naturally increase our confidence in this "negative" result.

Data from these same groups using the time of recurrence or metastasis, rather than death as the end point of treatment failure, are presented in Figure 2. Again no difference between the 5 FU adjuvant treatment group and control group is apparent.

The survival data from those patients with rectal cancer (less than 15 cm from the anal verge) are graphed separately in Figure 3. The total number of patients with rectal lesions appears too small for a reliable comparison of the 5 FU adjuvant treatment and control groups, but it is noteworthy that the constructed survival curves are similar to those calculated for the combined groups of colon and rectal lesions. Another selected subgroup of the whole, the Dukes' C lesions, was examined separately despite the small numbers of patients concerned. Again, there was no suggestion of benefit from adjuvant therapy noted (Table 7).

Discussion

It must be stressed that these results comparing "curative" surgery for colorectal cancer with and without adjuvant 5 FU therapy must be considered preliminary. There has been no demonstrated benefit for the group subjected to this lengthy adjuvant program following surgical resection, but the number of patients and the length of followup are both inadequate to clearly establish the fact that any possible difference is "contained" in a range that is of negligible ultimate benefit.

In view of the fact that there is good rationale for therapeutic value from adjuvant chemotherapy following "curative" surgery for cancer, it is prudent to consider possible factors that may have lead to our failure to demonstrate adjuvant benefit with this particular program of 5 FU. These factors include the choice of the chemotherapeutic agent itself, the total dosage administered in the postoperative interval, the actual schedule or method of drug administration, as well as other aspects of the conduct of the study. It is also conceivable that a subgroup of patients from the total study may have demonstrated benefit from this approach but that this has been obscured by consolidation of all subgroups into the two major categories. These concerns will be discussed separately.

The choice of the chemotherapeutic agent for an adjuvant chemotherapy program is dependent on the current information on tumor-drug relationships available to us from the use of chemotherapeutic agents in patients with advanced cancer. Although the response rate of advanced colorectal cancer to 5 FU is low (in the 20% range), there is no single agent with proven benefits for

TABLE 5. Total Oral Dosage Received by Adjuvant Chemotherapy Group in First Postoperative Year of Clinical Trial*

Total Oral Dosage	Total Group	Colon Cancer	Rectal Cancer	Colon & Rectal Cancer	
				Dukes' A & B	Dukes' C
> 80%	44/75 (59%)	26/46 (57%)	18/29 (62%)	30/50 (60%)	14/25 (56%)
> 60%	54/75 (72%)	34/46 (78%)	20/29 (69%)	36/50 (72%)	18/25 (72%)
> 40%	58/75 (77%)	35/46 (76%)	23/29 (79%)	38/50 (76%)	20/25 (80%)
< 40%	17/75 (23%)	11/46 (23%)	6/29 (21%)	12/50 (24%)	5/25 (20%)

* 75 patients >1 year postop.

TABLE 6. Incidence of Toxicity From Postoperative Oral 5 FU in Adjuvant Chemotherapy Group of Clinical Trial

	No. with Toxicity/ Total (%)	
Intraluminal and Immediate Postop IV 5 FU	0/80	
Oral 5 FU		
Colon cancer cases	18/49	(37%)
Rectal cancer cases	11/31	(35%)
Total	29/80	(36%)
Nature of toxicity:		
Leukopenia only -	21	
G I Only -	7	
Leukopenia and G I -	1	
Total	29	

colorectal cancer that is superior to 5 FU at present. It is also quite possible that the responsiveness of minimal residual (*i.e.* microscopic) disease is greater than the response rate for gross recurrent disease.

Using the dosage schedule and total dosage of 5 FU used in this study, the majority of patients, though not all, have tolerated this dose level given by intermittent courses. The toxicity observed gives some degree of confidence as to the adequacy of drug dosage for this adjuvant trial, even though the guidelines for toxicity and dose reduction are admittedly conservative in contrast to the levels of toxicity used for protocols that are applicable to established or advanced disease. It is generally agreed, however, that life endangering toxicity from adjuvant chemotherapy is not justified in patients with a reasonable chance for permanent control for their cancer.

Another possible objection to this program is the use of the oral route of drug administration rather than the more commonly used intravenous medication. Studies on plasma concentrations of 5 FU after peroral administra-

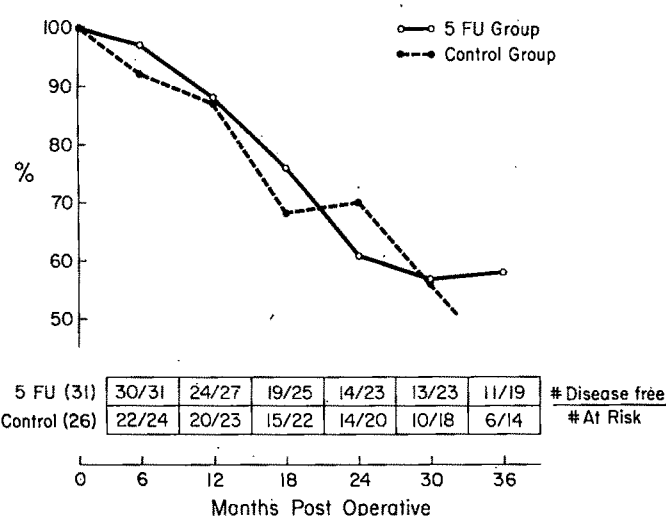


FIG. 3. Rectal cancer. Survival free of recurrence after "curative" resection (all stages).

tion show that peak plasma levels occur rapidly but are generally lower than seen after intravenous administration of comparable doses. There is also more variability in absorption than with intravenous administration but responses of established disease do occur and the toxicity observed is similar with both routes of administration.¹

The actual dosage schedule used in this study is an intermittent one rather than continuous weekly administration of agent at a lower dose level. The latter approach has not been shown to be better than the more commonly accepted loading dose technique but it is virtually impossible to assess the importance of variations in dose scheduling at this time. The ongoing long term postoperative adjuvant trial of 5 FU by the Central Oncology Group uses the chronic weekly administration of 5 FU and the results in this study may eventually provide an answer to this question. The COG Study appears to suggest some improvement in survival statistics in the 5

TABLE 7. Survival and Recurrence Free Survival Data for Patients with Dukes' C Lesions in 5 FU Adjuvant Trial

		Followup Period (Mos.)							
		6	12	18	24	30	36	42	48
5 FU Group	Proportion Surviving	25/25 (100%)	22/23 (96%)	17/20 (85%)	12/19 (63%)	10/19 (53%)	8/16 (50%)	6/12 (50%)	6/11 (55%)
	Proportion Free of Disease	22/25 (88%)	17/23 (74%)	12/20 (60%)	8/19 (42%)	8/19 (42%)	6/16 (38%)	5/12 (42%)	5/11 (45%)
Control Group	Proportion Surviving	27/28 (96%)	24/27 (89%)	22/26 (85%)	19/24 (79%)	16/23 (70%)	10/18 (56%)	6/13 (46%)	4/12 (33%)
	Proportion Free of Disease	26/28 (93%)	22/27 (81%)	21/26 (81%)	18/24 (75%)	14/23 (61%)	10/18 (56%)	6/13 (46%)	4/12 (33%)

FU adjuvant arm of this particular protocol, but the difference between the adjuvant and control groups is not statistically significant at this time (See addendum).

The remaining concern regarding this trial of adjuvant 5 FU for colorectal cancer is the possibility of "burying" an advantage from this approach in the subgroup of the whole by focusing on a comparative analysis of the total colorectal group with and without the adjuvant. The rectal and colon lesions were actually randomized separately to allow homogeneity and this fact will be used at a later date to conduct separate analyses by site when the numbers of patients involved are larger, and the followup period longer. Although the rectal lesions in the ongoing multihospital study in New York have somewhat better results in the adjuvant 5 FU group (as opposed to no difference with colon lesions) this difference is far from statistical significance.⁴ It is of interest that the small groups of rectal cancers in our study have grossly identical survival curves thus far despite a more prolonged course of adjuvant 5 FU therapy than used in the New York Study.

The initial studies of Rousselot and coworkers⁷ using historical controls seemed to indicate benefit from adjuvant 5 FU with colorectal lesions in patients in a higher risk category (Dukes' C). However, the current prospective clinical trial from this same group fails to even suggest this difference and our data are in agreement with this latter finding. One might conclude from all of these incomplete data that any real difference between adjuvant and control groups in a subcategory of the whole must be relatively small, or it would have been more apparent in the data that have been presented.

Conclusions

From our findings to date, we do not believe that the benefit of prolonged adjuvant therapy with 5 FU for patients undergoing "curative" surgery for colorectal cancer is adequate to justify its general use. In time,

minor degrees of benefit from this approach might become evident for all patients, or for patients in selected subgroups, but further evaluation to substantiate this must be accomplished before this approach can be recommended. Future trials of adjuvant chemotherapy for colorectal cancer may be more justified with a combination of chemotherapeutic agents or hopeful new agents, or immuno-adjuvants that are found to be effective for recurrent large bowel cancer.

Addendum

Since submission of this manuscript the results showing benefit from adjuvant 5 FU in the COG study have become statistically significant (Grage, T. E.; personal communication). It is of interest that the COG study differs from ours both in route of drug administration (intravenous) and scheduling of maintenance 5 FU (single weekly dose).

Acknowledgments

We are grateful to Saul Kay, M.D. (Professor of Pathology, MCV) and M. Shannon Allen, M.D. (Professor of Pathology, U. Va.) for review of the pathological material in this study. We are also thankful to Ms. Tina Bear and Ms. Nine Barnes for assistance in collecting the data and Dr. Roger Flora, Associate Professor of Biometry, MCV, for statistical evaluation of the data.

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DISCUSSION

(Note: Some of the discussants' remarks relate to both this paper and the following one by Dr. George Higgins. Such discussions follow both articles in this volume.)

DR. MURRAY M. COPELAND (Houston, Texas): The results of the study by Dr. Lawrence and his colleagues are in keeping with the results of other studies using 5-FU as an adjuvant to curative resection for colorectal cancer. The important difference between this study and a well-known study by the VA group which Dr. Higgins has been considerably involved in is that more intensive and longer duration of 5-FU was used in Dr. Lawrence's study. Nevertheless, on the basis of these studies it seems reasonable to conclude that 5-FU, given by itself, is probably not beneficial in prolonging the disease-free interval for patients who have had curative resections for colorectal cancer.

A study presently being conducted by Dr. Mavligit and Dr. Freireich at our institution is one in which BCG, therapy as an adjuvant to curative resection for colorectal cancer is being used. Although it

is too early to draw significant conclusions or to compare this study with that of Dr. Lawrence, there is a suggestion that early recurrence is less frequent with the use of BCG therapy. Thus, it is exciting to consider the possibility that immunotherapy or combinations of immunotherapy and chemotherapy might have significant advantages as adjuvants to curative surgical resection of colorectal cancer.

The findings in the report by Dr. Higgins and his group are of interest, and strongly suggest that preoperative radiation is worthwhile in patients who have rectal and low sigmoid primary lesions. It is important to emphasize that Dr. Higgins' results, as reflected in the survival curves for patients who have had curative resections, may be more significant than indicated. This is because patients who had curative resections following radiotherapy could have a worse prognosis than patients who had curative resections in the control group. Thus the difference in the survival curves might be more significant, taking this into account.

The major concern is that the sites and extent of recurrences, I don't believe, are discussed, Dr. Higgins. Perhaps I'm wrong about that. I

read your paper over quickly. The incidence of recurrence would be of great interest. In particular, a decreased incidence of local recurrence could be the best indicator of the effectiveness of preoperative radiation therapy.

The advantage of preoperative versus postoperative radiation is controversial for these low-lying lesions. Studies are presently being conducted which in the future can be compared to this study to determine the relative value of preoperative versus postoperative radiotherapy.

Dr. LOREN J. HUMPHREY (Kansas City, Kansas): If one looks at the change in survivals of carcinoma patients over the last 50 years, there has been progress in the field in general. Improvement has come from three areas: early detection; more precise staging, as with Hodgkin's disease; and, as in the recent data with sarcomas, combined radical therapy.

The points I would like to address to these two papers are that the basic problem, it would appear, with the adjuvant chemotherapy may be the problem of dosage and immunosuppression. Dr. Lawrence and his group are very well aware of these problems, and I only rise to emphasize from a study Dr. Jewell and I have done, that while the survival data are too recent to give meaningful data, the data does favor the combined immunotherapy and chemotherapy group. Antibody studies of serum from these patients, however, do show that those patients having antibody before chemotherapy become antibody negative after; whereas with immunotherapy, an additional 50% had antibody. So it appears that we are going to have to find the proper dose of chemotherapy if it is to be adjuvant.

The reason I rise to make the point about staging is my concern with radiation therapy, although one must endorse and support this type of randomized study. However, if one were to accept the fact that the nodal incidence were the same in the VA study, one would have to entertain that the low dose of radiation therapy indeed eliminated cancer in the lymph nodes giving the difference in incidence of metastatic disease in lymph nodes.

The problem, then, is severe; we lose a very important aspect of cancer management: proper staging; we do not know the stage of a

significant number of those patients. I believe in the future that we will need this staging to decide whether to go along with just surgery or whether to add postoperative radical radiation therapy or chemotherapy.

My question to Dr. Lawrence is: Are you going to use a much lower dose, or randomize treatment into two different doses?

Dr. J. SHELTON HORSLEY, III (Closing discussion): There are several points I would like to re-emphasize in Dr. Lawrence's presentation. One is the use of the word "preliminary." This in a way answers the question Dr. Humphrey asked: Are we going to change our dosage? Actually, this has been submitted to statistical analysis, and our statistician tells us that to increase the confidence in our results we should follow these patients for another three to four years, which we plan on doing, and hope we will have the privilege of presenting those data in the not-too-distant future.

Also, someone might ask: How about Dukes' C patients? Is there any difference? Certainly in Rousselot and Grossi's work the most striking differences were in Dukes' C patients. In our patients the Dukes' C showed no difference between those in the 5-Fluorouracil and those in the control group.

We administered the drug orally postoperatively for patient convenience. We feel that this was a satisfactory way to administer the drug, as witnessed by the fact that we did get some toxicity. I don't think it was a homeopathic dose. It was well tolerated by the patient. It was taken orally in orange juice or water.

I appreciate Dr. Copeland's remarks. We have had no experience with BCG, but we follow his leadership in this national study, and we look to him for suggestions of other modes of therapy that perhaps will be more effective.

As Dr. Humphrey has pointed out, one of the problems in this type of study may be the proper dose. We are not sure what the proper dose is under these circumstances, and look for help from him and other groups regarding their immunologic studies that perhaps will pin down what is and what isn't a proper dose.

Preoperative Radiotherapy for Colorectal Cancer

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In a prospective randomized trial, 700 patients with a confirmed histologic diagnosis of adenocarcinoma of the rectum or rectosigmoid were randomized to receive radiotherapy prior to operation (2000 to 2500 rads in two weeks) or surgery alone. Five year observed survival in the 453 patients on whom "curative" resection was possible was 48.5% in the X-ray treated group compared with 38.8% in controls, while in the 305 having low lying lesions requiring abdominoperineal resection, survival in the treated group was 46.9% compared with 34.3% in controls. Although suggestive of a treatment benefit, neither is considered statistically significant. Histologically positive lymph nodes were found in 41.2% of the control group and in only 27.8% of the patients receiving radiotherapy. Review of all patients who died during the study shows a consistently lower death rate from cancer in the radiotherapy group. Although this study suggests a treatment benefit from preoperative radiotherapy, further studies now in progress by this group and others are necessary to determine the optimal dose regimen.

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1974, Boca Raton, Florida.

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CANCER of the large bowel, with essentially equal sex distribution, has an incidence in the total United States population surpassed only by skin cancer. During the past two decades there has been an increasing effort to improve long term survival by employing adjuvant chemotherapy or immunotherapy or by the use of radiotherapy to supplement what are now fairly standardized surgical techniques. The first reported incidence of the use of preoperative radiotherapy in cancer management is contained in a brief paper published in 1914 by Symonds¹⁵ of London, describing the application of radium bromide to a low lying carcinoma of the rectum with marked regression of the lesion and apparent successful surgical resection some three months later. Despite this encouraging report, only sporadic publications on the use of preoperative radiotherapy occurred during the next 45 years and very little interest in this approach was generated until the publication in 1959 of a retrospective study of experiences at the Memorial Hospital for Cancer and Allied Diseases of New York.^{2,14} In this review, a group of patients, usually with advanced carcinoma of the rectum, treated with a somewhat variable regimen of radiotherapy (average calculated tumor dose not exceeding 2000 rads) were compared with a similar group of patients treated by surgery alone. Results of this retrospective study suggested a substantially improved 5-year survival rate in those patients who had received preoperative radiotherapy, principally those with Dukes C lesions. In March 1964 the Veterans Administration Surgical Adjuvant Group began a prospective randomized trial designed to examine more carefully the possible benefit of preoperative radiotherapy in patients with carcinoma of the rectum and rectosigmoid. By Feb-

ruary 1969, when accession of cases was discontinued, 700 patients had been entered into the study. It is now possible to review 5-year observed survival data in the study and to examine extended survival figures for the 5- to 10-year interval.

Materials and Methods

All male patients with adenocarcinoma of the sigmoid or rectum proved by sigmoidoscopic biopsy who were believed preoperatively to have resectable lesions were considered for the study. Evidence of distant metastases was not a reason for exclusion if a palliative resection of the primary lesion appeared possible and advisable. Patients with a previous diagnosis of carcinoma were not included. When a positive histologic diagnosis was secured and informed consent obtained, each patient was allocated at random to treatment or control groups on the basis of a sealed envelope provided by the statistician. Those patients randomized to the control group were operated upon as soon as feasible, whereas those in the treatment group were given irradiation therapy followed by operation. On the basis of operative findings patients were divided into clinically "curative" or "palliative" categories. Following thorough review of the specimen by the pathologist, a final designation of "palliative" or "curative" was made, depending upon microscopic evidence of tumor at a resection margin or metastases left behind.

Dosage and Plan of Irradiation Therapy

When the protocol was proposed a panel of radiotherapists was consulted in an effort to determine the proper dosage and treatment plan to accomplish the desired effect without increasing postoperative mortality and morbidity. Members of the radiotherapy advisory panel¹² offered plans for both a "high dosage protocol" and a "low dosage protocol." All surgeons in the study group, however, elected to use only the low dosage regimen.

At the onset of the study, not all hospitals in the group had ready access to high energy radiotherapy equipment. For this reason, the protocol permitted the use of either conventional orthovoltage machines or supervoltage x-ray or Cobalt 60 units. Since the early phase of the study, practically all patients were treated with supervoltage equipment. The radiation therapy was administered to the entire pelvis through anterior and posterior paired opposing portals, 20 x 20 cm each, from the anus up to the brim of the bony pelvis. A tumor dose of 2000 rads was delivered to the midplane of this volume, generally 10 cm in depth, employing 10 daily fractions of 200 rads each. When the tumor was found to be at a level of 8 cm or closer to the anal verge, a booster dose of 500 rads (10 daily fractions of 50 rads each) was to be delivered through a perineal portal approximately 10 x 10 cm. Op-

TABLE 1. *Operative Status of 700 Patients*

	Treated		Control		Total
	No.	%	No.	%	
Total patients	347	100 %	353	100 %	700
No operation	17	4.9%	3	0.8%	20
Non resectable	28	8.1%	39	11 %	67
Resection	302	87 %	311	88 %	613
Anterior	89	26 %	94	27 %	183
Abdominoperineal	206	59 %	208	59 %	414
Other	7	2 %	9	2.5%	16

eration was then carried out at any time after completion of the irradiation.

Early Results

Despite previous reassuring reports, there was considerable concern by surgeons in the study that the radiotherapy might compromise surgical dissection, delay wound healing, or in some other fashion lead to an increase in operative mortality and morbidity. For this reason, incoming data were continually monitored by the statistical office. Indeed as reports began to accumulate in the early phases of the study, this apprehension was heightened by a substantially greater 30 day postoperative mortality in those patients receiving preoperative radiotherapy than in the control group. However, careful review of each operative death failed to suggest any relationship with radiotherapy, and because of this and data accumulated in numerous previous protocols, the members of the group elected to proceed with the trial. As reported previously,⁷ this decision was vindicated when accrual of a larger number of patients showed comparable morbidity and mortality in the two randomized groups.

Operative status of the 700 patients randomized into the study is shown in Table 1. Careful analysis of factors such as age, race, extent of disease and location of the lesion showed no discrepancies in comparability between the 347 patients randomized to receive x-ray and the 353 serving as controls. As would be anticipated, more patients did not come to operation in the treated group because of death of the patient during therapy, decision of inoperability upon re-evaluation following therapy, or refusal of the patient to accept therapy. The resectability rate was essentially the same in the two groups. There were 414 abdominoperineal resections, 183 anterior resections, and 16 "other" including subtotal colectomies, pull-throughs and Hartmann procedures, the incidence being the same in treated and control groups.

Long Term Survival

Since all patients entered into the study have been at risk for a minimum of 5 years, observed 5-year survival data have now been completed. Of the 700 patients en-

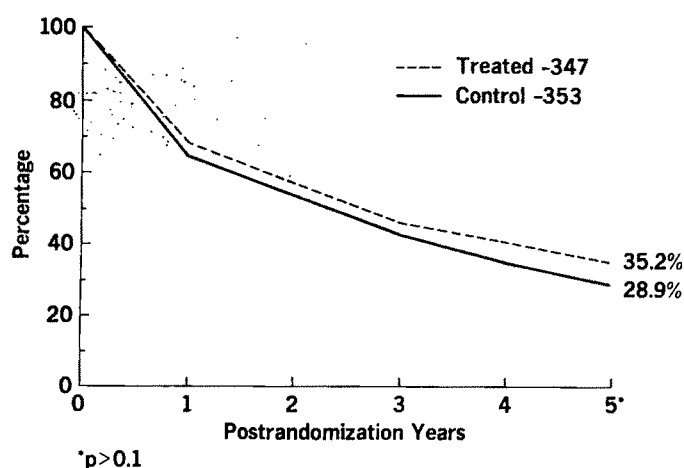


FIG. 1. Observed 5 year survival in 700 patients entered into the trial.

tered into the trial, a total of 244 were living and under observation 5 years following randomization. The 5-year survival curve for this group of patients is shown in Figure 1. While survival in the treated group (35.2%) compared with the control group (28.9%) is not statistically significant ($P > 0.1$) * it does suggest a more detailed examination of selected groups of patients in the trial. Survival curves for the 613 patients on whom resection was possible is shown in Figure 2, 5-year observed survival being 40.1% in those patients receiving radiotherapy compared with 32.2% in those having operation alone. In 453 of these patients, the resection was considered to be clinically "curative" (no gross evidence of residual disease or metastases), 5-year observed survival in the x-ray treated group being 48.5% as compared with 38.8% in the control group (Fig. 3). Although these data suggest a possible treatment benefit, neither difference is considered statistically significant ($0.1 > P > 0.05$). In the study design, all lesions within reach of the sigmoidoscope for biopsy determination were included.

*All P-values on survival curves obtained by Haenszel-Mantel test.

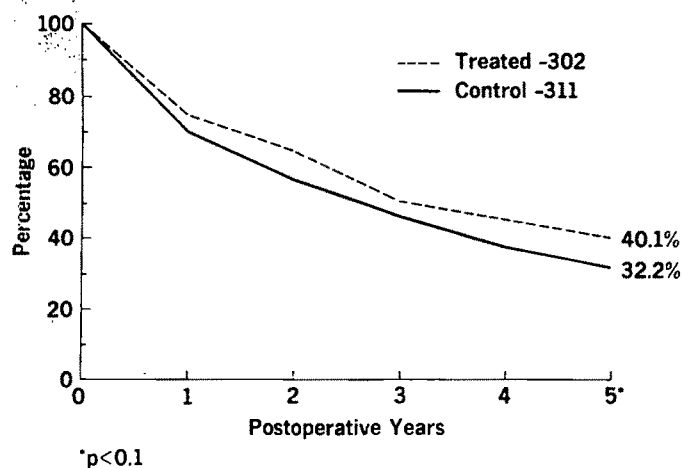


FIG. 2. Observed 5 year survival in 613 patients on whom resection was possible.

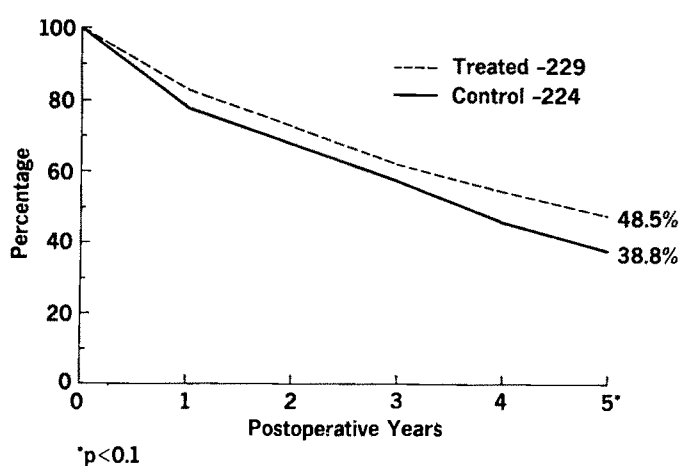


FIG. 3. Observed 5 year survival in 451 patients in the trial on whom "curative" resection was possible.

As indicated in Table 1, in 183 patients, the lesion was sufficiently proximal to permit an anterior resection, while in 414 abdominoperineal resection was the procedure used. A small number (16) had miscellaneous other types of operation. Survival curves for patients having abdominoperineal resection are shown in Figure 4. Observed survival of 40.8% in the treated group compared with 28.4% in the control group is highly suggestive of a treatment benefit ($0.02 > P > 0.01$). In the remaining patients having other types of resection there is an identical 5-year survival in treated and control groups (38.5% and 39.8%). Thus the entire difference in survival shown in Figure 2 can be attributed to patients having the lower lying lesions. Benefit from radiotherapy might be anticipated to occur primarily in patients on whom "curative" resection could be accomplished. Survival data on the 305 patients in this category is shown in Figure 5 (46.9% in the treated group compared with 34.3% in controls). This again is suggestive of a treatment benefit but not statistically significant ($0.1 > P > 0.05$).

The finding of a suggested treatment benefit being con-

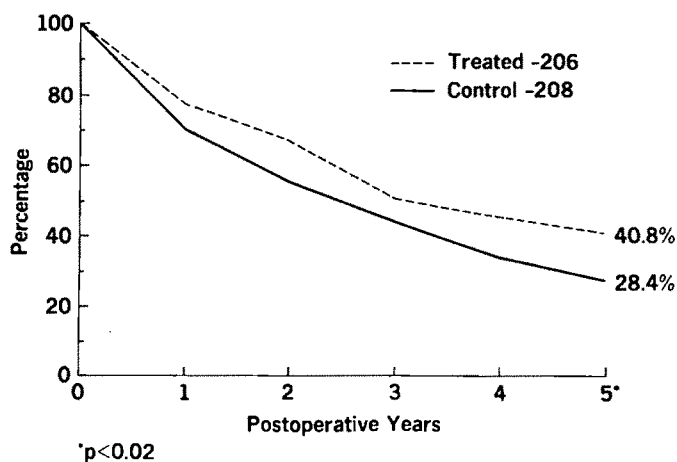


FIG. 4. Observed 5 year survival in 404 patients having abdominoperineal resection.

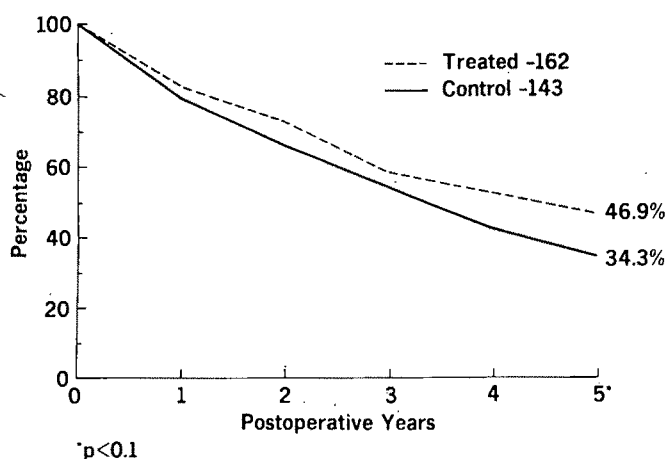


FIG. 5. Observed 5 year survival in 305 patients having abdominoperineal resection on whom no residual or metastatic disease was apparent at the time of resection.

finer to those patients with the more distal lesions requiring abdominoperineal resection while not anticipated was not surprising on theoretical grounds. Since the rectum is closely encased by a narrowing pelvic funnel, lesions in this area are comparatively fixed permitting the radiotherapist to center the x-ray beam in the region of the tumor. Lesions above the perineal reflection being located in the comparatively mobile sigmoid are not easily localized by the radiotherapist and may vary somewhat in position because of peristaltic activity of the sigmoid. Also the protocol provided that an additional 500 rads be administered to a perineal port in those patients with lesions below 8 cm from the anal verge. Data from the study, examined in an effort to determine any relationship of total dosage to survival as well as a similar analysis directed to any difference attributable to energy level of the radiotherapy units employed, revealed no remarkable differences.

Interval and Extended Survival

Data accumulated in the study were evaluated further by using life table procedures to estimate survival beyond the fifth year and by calculating interval survival (the

percentage of patients alive at the start of each successive followup interval who survived the interval). These data for the 305 patients who underwent "curative" abdominoperineal resection (the group showing suggestive benefit from radiotherapy) are shown in Table 2. Survival at the 9 year postoperative period is quite similar in the treated and control group (24% versus 21%). Since survival at the 5-year period for those patients having radiotherapy was 47% compared with 34% for the control group, it is apparent that survival from the fifth to the ninth followup years is somewhat better in the control group. With relatively small numbers of patients involved, it cannot be concluded that treated patients are at a disadvantage beyond the fifth postoperative year, but there is no evidence that any appreciable benefit persists.

Examination of the interval survival figures shows that during the first 3 postoperative years, there was no appreciable difference between the treated and control group of patients. However, among patients who were still living 3 years postoperative, 93% of the treated patients survived an additional year compared with 75% of controls, while 88% and 83% respectively, survived the fifth postoperative year. Thus, the apparent benefit in survival in the treated group appears to occur predominantly between the third and fifth postoperative years.

A delayed benefit to patients receiving radiotherapy is not an unreasonable possibility. If preoperative radiation were to reduce the hazard of spreading tumor cells during the increased manipulation at the time of operation by destroying the cells or by lowering their viability, then the benefit would not become apparent until enough time had elapsed for implants to develop to lethal size in those patients not receiving radiotherapy. Presumably the majority of cancer deaths within 3 years of resection would be due to pre-existing but unrecognized metastases. If one wished to carry this reasoning further, in the absence of evidence of an improved survival from the radiotherapy beyond 5 years resulting from slower growing rather than reduced numbers of metastatic lesions, then a period of increased survival in treated patients compared with controls could be followed by one of reduced survival as the slower growing metastases reach life threatening size.

Lymph Node Involvement

Since the Memorial Hospital Study had shown improved survival to be confined to patients having Dukes C lesions, data from this study were carefully reviewed regarding this factor.⁶ The Dukes classification was not used in the Veterans Administration Study although detailed information on the pathologist's findings were recorded and tabulated. Table 3 contains 5 year survival data in the 453 patients having "curative" resection based on whether or not radiotherapy was given, the presence or absence of involved lymph nodes in the specimen, and the type of operation performed. The suggested treatment benefit is seen to occur primarily in

TABLE 2. Interval Survival: "Curative" Abdominoperineal Resection

Postop interval (yrs)	Treated	Control
0-1	82%	78%
1-2	87%	85%
2-3	79%	83%
3-4	93%	75%
4-5	88%	83%
0-5	47%	34%
5-9	51%	61%

TABLE 3. Five Year Survival by Treatment Status, Type of Operation and Presence of Positive Lymph Nodes, "Curative" Resection Only

		Treated	Control
Total Resections	(453 pts)*	48.5%	38.8%
Lymph Nodes Positive	(122 pts)	38.0%	26.4%
Lymph Nodes Negative	(327 pts)	51.4%	45.3%
Abdominoperineal	(305 pts)*	46.9%	34.3%
Lymph Nodes Positive	(87 pts)	32.4%	24.0%
Lymph Nodes Negative	(216 pts)	51.2%	39.8%
Other Resections	(148 pts)*	52.2%	46.9%
Lymph Nodes Positive	(35 pts)	53.8%	31.8%
Lymph Nodes Negative	(111 pts)	51.9%	54.4%

*Status of nodes unknown in four patients.

those patients having abdominoperineal resection (also shown in Fig. 5). Treatment benefit is seen in this group in both patients with positive nodes and those whose nodes were negative. In the 148 patients having other types of resection (principally anterior resection), survival figures are essentially the same. Although percentage survival in this group with positive lymph nodes is higher in those having radiotherapy (53.8% compared to 31.8%) the number of patients is too small for statistical significance.

This analysis of data pertaining to lymph node involvement, however, provided some interesting and provocative information (Table 4). As indicated, positive lymph nodes were found in only 27.8% of the specimens resected in patients who received preoperative x-ray therapy, as compared to 41.2% in the control group. This decrease in positive lymph node involvement in the x-ray treated patients was greater in the low lying lesions requiring abdominoperineal resections (26.2% versus 44.2%) although it was also observed in patients having other types of resection (31.2% versus 35%). A review also showed similarity in the number of specimens in which lymph nodes not involved with tumor were reported, thus indicating consistency in the diligence of the pathologist in searching for nodes. Data were also studied to determine whether the finding of involved lymph nodes was related to the fields used in treatment or with the dose of x-ray administered to the tumor. The percentage of positive lymph node involvement was con-

sistently lower in patients receiving higher tumor dosage though not statistically significant.

Members of the group have found it difficult to believe that irradiation therapy administered in this dosage and in this fashion, with operation carried out immediately following the completion of therapy, could destroy tumor cells in the adjacent lymph nodes. Likewise, pathologists who studied the specimens reported no histologic evidence of dying or "ghost tumor cells" in lymph nodes or any other evidence to suggest the destruction of tumor cells in nodes. Nevertheless, this suggestive evidence that preoperative radiotherapy might possibly destroy foci of tumor cells in lymph nodes adjacent to the tumor site with conversion to a much more favorable stage of disease, is one which merits further study and investigation.

Cause of Death

Case records of all patients who died either in the early or remote postoperative period were carefully reviewed in an effort to determine the cause of death and in particular whether or not there was evidence of recurrent or metastatic cancer present. A summary of 461 patients who had microscopically "curative" resection (no evidence of tumor in biopsy of other areas or at resection margins) and who have died since being entered into the study is contained in Table 5. These patients were chosen because any beneficial effect from radiotherapy should be observed in this group. Review of all available material in the case record was made by the site chairman and the decision made as to whether death could be attributable to cancer. The percentage of patients dying of cancer is smaller in those patients having preoperative radiotherapy than in those treated by surgery alone in both the abdominoperineal resection category and those having other types of resection. These differences in favor of the treated group are not statistically significant but suggest that radiotherapy may increase prospects of survival.

Complete autopsy results were available in 180 of these patients (Table 6). These data show a consistently smaller percentage of evidence of cancer at autopsy in those patients receiving radiotherapy than in control patients ($0.05 > P > 0.02$). These figures are more pronounced when examined for the presence of metastases than for the presence of local recurrence.

Discussion

While detailed review of the theoretical and technical aspects of radiotherapy prior to operation is not the pur-

TABLE 4. Lymph Node Involvement in Resected Specimens

	Treated		Control	
	No.	%	No.	%
All resections	84/302	27.8	128/311	41.2
"Curative"	50/229	21.8	72/224	32.1
Palliative	34/73	46.6	56/87	64.4
A. P. resection	54/206	26.2	92/208	44.2
"Curative"	37/162	22.8	50/143	35.0
Palliative	17/37	45.9	42/59	71.2
Other resection	30/96	31.2	36/103	35.0
"Curative"	13/67	19.4	22/81	27.2
Palliative	17/29	58.6	14/22	63.6

TABLE 5. VASAG: Preoperative Radiotherapy-Colorectal CA, "Curative" Cases Only-Deaths Attributable to Cancer

	Total	A-P Resection	Other
Treated	113/220 (51%)	83/155 (54%)	30/65 (46%)
Control	142/241 (59%)	103/167 (62%)	39/74 (53%)

pose of this presentation, a brief consideration of the rationale of this approach as well as an outline of the major studies now in progress is in order.

The primary objective in administering radiotherapy prior to operation is to modify the malignant cells so that those dislodged either into the lymphatics or blood stream or implanted into the operative field will not be able to survive as metastatic implants or local recurrence. Of course if malignant cells already spread beyond the bowel wall into lymphatics and local lymph nodes can be destroyed or rendered incapable of further growth, this would in effect convert the lesion from a Dukes C to a Dukes B classification with presumably a much more favorable prognosis. Yet another desirable goal of radiotherapy might be the conversion of an inoperable to an operable lesion by the shrinkage of a large bulky tumor mass. In certain situations such as patient refusal to accept operation or the presence of medical contraindications to surgery, radiotherapy might be employed as the definitive curative therapy.

In considering the use of preoperative radiotherapy, one must not only be concerned with the total dosage but also the time interval used to deliver the prescribed number of rads. If a small or moderate dosage is used, the operation may be carried out immediately upon the completion of radiotherapy, whereas a delay of several weeks is necessary following completion of a large dose of radiotherapy if serious tissue breakdown and delay in healing is to be avoided. At present a fairly wide dose range is being used by the various centers using preoperative radiotherapy. Papillon of France⁹ administers radiotherapy directly to the lesion through a sigmoidoscope-like device using low voltage equipment. Only superficial lesions that have not spread beyond the bowel wall are considered appropriate for this technique which has been used as either definitive therapy or as preoperative therapy for certain patients. At the Princess Margaret Hospital in Toronto, a small randomized study has been carried out using 500 rads through conventional ports in the immediate preoperative period.¹⁰ Preliminary analysis of this study has suggested a possible benefit to those patients randomized to the treatment group. A three arm protocol has been proposed comparing surgery alone, irradiation followed by surgery, and high dosage radiotherapy administered for cure. In a recent publication,¹³ results of the randomized study conducted at Memorial Hospital in New York were reported. In patients randomized to receive radiotherapy, a dosage of 2500 rads was administered over a two week period with operation to follow immediately. No benefit from therapy was found in the analysis of the 5 year determinate survival rate. It appeared that local recurrence rate was reduced in the treated group but this was offset by an increase in failure from distant metastases. There was also a suggestion that male patients might benefit from the treatment. Antunez of the Cleveland Clinic¹¹ reports

TABLE 6. VASAG: Preoperative Radiotherapy-Colorectal CA, "Curative" Cases Only—Presence of Cancer at Autopsy

Total (180)		A-P Resection (122)		Other Resection (58)	
Treated 49%	Control 68%*	Treated 50%	Control 70%*	Treated 49%	Control 61%
29%	36%	Local Recurrence 29% 40%		29%	26%
46%	62%	Metastases 47% 63%		44%	60%

*P<0.05

a small series using a dosage of 800 rads daily for 3 days for a total of 2400 rads with operation performed 10-15 days later. This technique was used in an attempt to accomplish in cancer of the rectum what the "no touch isolation resection technique" used at that institution theoretically achieves in carcinoma of the remainder of the large bowel, the prevention of dissemination of viable cancer cells at the time of operation. The number of patients reported is small but the authors state that "results compare favorably with those reported in the literature."

For a number of years, both the University of Oregon and Yale Medical Center have used high dosage radiotherapy prior to operation. Allen, Fletcher and Dunphy^{1,4} at the former institution employ either Cobalt 60 teletherapy or a 2 mev VandeGraaff generator to deliver 5000 rads at the rate of 900 rads per week using a small field (usually 10 x 10 cm). Operation, usually abdominoperineal resection, was done 5 to 6 weeks following completion of irradiation. Most of the patients in this small uncontrolled series had advanced disease but survival figures compare favorably with those of another hospital as well as with historical controls from the same institution. Of particular interest was the finding that there was no evidence of viable tumor in 10% of the surgical specimens and only *in situ* carcinoma in an additional 10%. At the Yale New Haven Hospital,⁸ a 6 mev linear accelerator was used to deliver 4500 rads in 4½ weeks using a field to encompass the primary tumor as well as the adjacent tissue and the lymph node drainage in the pelvis and to the level of the second lumbar vertebra. Operation was scheduled one month after the end of radiation treatment. Following a small pilot study, a randomized protocol was begun. Accrual of patients in the randomized study has been slow partially because many of the participating surgeons have elected to use preoperative radiotherapy rather than enter their patients into the study. A detailed analysis of the operative specimens has suggested that a number of the lesions may have been converted from Dukes C to Dukes A or B lesions although the ultimate effect on survival is as yet undetermined.

Three large cooperative groups are now conducting trials of operative radiotherapy for rectal cancer. The

Central Oncology Group and Radiotherapy Oncology Group (COG-ROTG)³ are using a three arm study comparing surgery alone with low dose therapy (2000 to 2500 rads over a 2 week period) and high dose therapy (4000 to 4600 rads over a 5 week period). When low dose therapy is used the operation is carried out upon completion of radiotherapy. Following the high dosage regimen, operation is carried out from 3 to 5 weeks following completion. Only a small number of patients have been entered into the study. The European Organization for Research on Treatment of Cancer (EORTC) with headquarters in Brussels,⁵ uses 3450 rads in a period of 18 days with surgery to be carried out within 2 weeks following completion of radiation. In this study, surgery alone is not used as a control but a second arm of the protocol adds chemotherapy with 5FU to radiotherapy prior to operation. At this time approximately 100 patients have been entered into the trial but sufficient time has not elapsed to permit survival analysis. No evidence of tumor could be found by the pathologist in a number of resected specimens. Early in the study minor delay in healing of the perineal wound was observed in some patients.

In the protocol being used by the Veterans Administration Surgical Adjuvant Group at present, those patients having rectal carcinoma at a level requiring abdominoperineal resection are randomized. Using AP and PA inverted T portals to the level of the second lumbar vertebra, dosage of 175 rads per day are administered for 18 treatments over a 24 day period, the total dosage being 3150 rads. Operation is then carried out at any time following completion of the radiotherapy. This dosage, slightly less than that used by the EORTC study, falls midway between the two dosages being used by the COG-ROTG Group.

There is every indication then that radiotherapy used prior to standard operative treatment may improve survival; however, none of the studies yet completed have clearly demonstrated this benefit, and indeed, the Memorial randomized study failed to substantiate the optimistic

findings from the original nonrandomized review. Hopefully the presently ongoing trials will tell us how best to use this two-pronged attack for the ultimate benefit of our patients.

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DISCUSSION

(Note: Some of the discussants' remarks relate to both this paper and the preceding one by Dr. Walter Lawrence. Such discussions follow both articles in this volume.)

DR. MURRAY M. COPELAND (Houston, Texas): The results of the study by Dr. Lawrence and his colleagues are in keeping with the results of other studies using 5-FU as an adjuvant to curative resection for colorectal cancer. The important difference between this study and a well-known study by the VA group which Dr. Higgins has been considerably involved in is that more intensive and longer duration of 5-FU was used in Dr. Lawrence's study. Nevertheless, on the basis of these studies it seems reasonable to conclude that 5-FU, given by itself, is probably not beneficial in prolonging the disease-free interval for patients who have had curative resections for colorectal cancer.

A study presently being conducted by Dr. Mavligit and Dr. Freireich at our institution is one in which BCG therapy as an adjuvant to curative resection for colorectal cancer is being used. Although it is much too

early to draw significant conclusions or to compare this study with that of Dr. Lawrence, there is a suggestion that early recurrence is less frequent with the use of BCG therapy. Thus, it is exciting to consider the possibility that immunotherapy or combinations of immunotherapy and chemotherapy might have significant advantages as adjuvants to curative surgical resection of colorectal cancer.

The findings in the report by Dr. Higgins and his group are of interest, and strongly suggest that preoperative radiation is worthwhile in patients who have rectal and low sigmoid primary lesions. It is important to emphasize that Dr. Higgins' results, as reflected in the survival curves for patients who have had curative resections, may be more significant than indicated. This is so because patients who had curative resections following radiotherapy could have a worse prognosis than patients who had curative resections in the control group. Thus the difference in the survival curves might be more significant, taking this into account.

The major concern is that the sites and extent of recurrences, I don't believe, are discussed, Dr. Higgins. Perhaps I'm wrong about that. I read your paper over quickly. The incidence of recurrence would be of

great interest. In particular, a decreased incidence of local recurrence could be the best indicator of the effectiveness of preoperative radiation therapy.

The advantage of preoperative versus postoperative radiation is controversial for these low-lying lesions. Studies are presently being conducted which in the future can be compared to this study to determine the relative value of preoperative versus postoperative radiotherapy.

DR. CHARLES ECKERT (Albany, New York): Studies such as those reported by Dr. Higgins from the combined Veterans Administration hospital group are very important, but it is terribly important that we not be misled by the incorrect interpretation of the observed differences in survival and other parameters between the treated and the control groups.

I would like to ask whether there was histologic evidence of regression of metastatic disease in any of the lymph nodes examined in the treated group. Failing this direct evidence of radiation effect, I would interpret the difference in frequency of lymph node involvement between these two groups as indicative of a lack of comparability between the two groups.

Randomized trials are of value, but there is nothing magical about them that ensures that two populations will be comparable. Skewed data are all too frequent and a lack of comparability would explain the differences in survival that were observed. This is particularly likely, since the 138 difference in survival of patients with low-lying lesions requiring abdominal perineal resection is exactly the same as the difference in survival between the two groups.

Therefore, I interject this note of caution in interpreting this study as definitively demonstrating that preoperative radiotherapy is of value. I think these studies should be continued, as Dr. Higgins proposes to do, especially with a higher dosage group.

DR. LOREN J. HUMPHREY (Kansas City, Kansas): If one looks at the change in survivals of carcinoma patients over the last 50 years, there has been progress in the field in general. Improvement has come from three areas: early detection; more precise staging, as with Hodgkin's disease; and, as in the recent data with sarcomas, combined radical therapy.

The points I would like to address to these two papers are that the basic problem, it would appear, with the adjuvant chemotherapy may be the problem of dosage and immunosuppression. Dr. Lawrence and his group are very well aware of these problems, and I only rise to emphasize from a study Dr. Jewell and I have done, that while the survival data are too recent to give meaningful data, the data does favor the combined immunotherapy and chemotherapy group. Antibody studies of serum from these patients, however, do show that those patients having antibody before chemotherapy become antibody negative after; whereas with immunotherapy, an additional 50% had antibody. So it appears that we are going to have to find the proper dose of chemotherapy if it is to be adjuvant.

The reason I rise to make the point about staging is my concern with radiation therapy, although one must endorse and support this type of randomized study. However, if one were to accept the fact that the nodal incidence were the same in the VA study, one would have to entertain that the low dose of radiation therapy indeed eliminated cancer in the lymph nodes giving the difference in incidence of metastatic disease in lymph nodes.

The problem, then, is severe; we lose a very important aspect of cancer management: proper staging; we do not know the stage of a significant number of those patients. I believe in the future that we will need this staging to decide whether to go along with just surgery or whether to add postoperative radical radiation therapy or chemotherapy.

I wonder if Dr. Higgins could tell us if he thinks that 2000 r. really has the capability of sterilizing adenocarcinoma of the colon metastatic to lymph nodes.

DR. RICHARD G. MARTIN (Houston, Texas): I rise to make a few comments on our program at the M.D. Anderson Hospital in Houston.

Our radiotherapists will not treat colon or rectal carcinoma preoperatively unless they can give 4000 rads or more. They feel they cannot sterilize lymph nodes with the smaller doses and, therefore, will not do it.

We, as surgeons, have been reluctant to go to the high doses because of the complication rate following surgery.

We have been running carcinoembryonic antigen (CEA) tests—serial tests—on all our rectal and colon cases. We have found with chemotherapy, either BCG or straight chemotherapy, that we have not been able to lower the CEA levels appreciably. However, with high doses of x-ray therapy, in the range of 5000-6000 rads, we have seen a drop in the CEA level and, also, the local tumor has regressed tremendously with the high doses of radiation.

I would like to go along with Dr. Eckert's comments and would like to see a breakdown of the lesions in Dr. Higgins' two groups.

DR. GEORGE A. HIGGINS (Closing discussion): I have a couple of slides on adjuvant chemotherapy, since Dr. Lawrence mentioned our chemotherapy studies, that I think might be of interest, if I may show these.

(Slide) Here are two groups of patients in the study he mentioned, one that had proved residual disease left behind (palliative) and a group that were considered clinically palliative. The numbers are small as you can see—but again, in this particular study, those patients who received 5-FU, given until disease progressed, or until the patient died—there is a suggestion of a treatment benefit from the 5-FU.

In the next study we did, (slide) we started on what we termed a prolonged intermittent therapy. These patients were randomized, and then placed on therapy at six-week intervals for 18 months. This is unpublished material and is just now getting out far enough to have meaningful results. As you can see, it's the same dosage, essentially, that we used before, in over 500 randomized patients. In the curative group these survival curves are absolutely identical.

Now, if we go to the proved residual disease group, again we find a suggestion that those patients randomized to receive the drug did a little bit better.

In the two studies patients weren't exactly comparable, because in the second study we included rectal cases, whereas the first study included only colon because we were doing the x-ray study on the low-lying lesions at that time.

We excluded certain patients to get comparability and in the "curative" groups, survival is identical in both studies. However, in the palliative patients, we can see that there is a suggestion of a treatment benefit in the 5-FU group.

(Slide) We are now running a randomized study regimen, using Methyl CCNU by mouth, and then a reduced dosage of 5-FU concomitantly. Patients are treated at six-week intervals in the curative group for a one-year period of time. In Group B, the palliative group, we continue to treat until death or disease progresses.

Now, to get back to closing my paper, I appreciate the comments and questions of Dr. Eckert, Dr. Humphrey and Dr. Martin, which I will answer all in one, because they were directed toward the matter of lymph node metastases. I think I made it clear that I was probably the most skeptical of anybody about this. Dr. Martin said his radiotherapists stated that they would not use the low dosage because it would not sterilize nodes, and I don't know how they know that. I wonder if they have had any experience with this regimen.

I believe both Dr. Eckert and Dr. Humphrey asked if we found evidence of ghost cells and residual cells in the lymph nodes. These were not described. However, we did review this group of cases very carefully, and the total number of lymph nodes found and reported by the pathologist was the same. This indicated to us that there was no bias on the part of the pathologist. As a matter of fact, he had no way of knowing whether the patient had had radiotherapy or not, and really couldn't tell.

The other thing that I should mention is that in the slightly higher dose ranges, the pathologist may find no definite tumor in the specimen. In the group reported from Oregon, there were a fairly sizable group with no residual tumor. In the study that we are doing now with 3150 rads we have found a number of specimens with no tumor.

Professor Gerard from Brussels, who is a surgeon in the EORTC Group, has reported a number of patients with no tumor in the resected specimen. So, certainly, my feeling is that when we learn how to combine newer techniques of radiotherapy with surgery we're going to improve our survival.

And last, I thank Dr. Copeland for his discussion and plan to continue randomized studies.

Is Childhood Thyroid Cancer a Lethal Disease?

JOSEPH A. BUCKWALTER, M.D., COLIN G. THOMAS, M.D., JOEL B. FREEMAN, M.D.

The clinical, pathological, surgical, postoperative findings and survivorship of 58 patients younger and 513 patients older than 21 years at the time of diagnosis with thyroid neoplasms are reported. The younger patients have a predominance of well differentiated carcinomas which are more likely to be follicular. The lesions tend to be more advanced at the time of diagnosis, are treated by more aggressive surgery in the younger patients and are associated with a much better prognosis. Lack of progression of well to poorly differentiated neoplasms and a greater sensitivity to and dependence upon TSH in young patients, are two factors which may contribute to the striking difference in the prognosis of well differentiated thyroid carcinoma related to age.

NEOPLASMS of the thyroid are relatively rare (less than 1% of all malignant neoplasms) causing approximately 1100 deaths annually in the United States. Thyroid cancers vary in their biologic behavior. This is related to: 1) histology of the lesion, 2) stage of the disease, and 3) age and sex of the patient. Other important factors in prognosis which are more difficult to evaluate are: 1) hormonal dependence, 2) functional activity of the cancer, 3) initiating and promoting factors, and 4) the immunologic and endocrine status of the host. All of these determinants of prognosis are probably inter-related.

The most important prognostic factor in a patient with a thyroid neoplasm is histology. Three groups of neoplasms of the thyroid can be defined on the basis of their biologic behavior and the differing clinical course of patients. These are: well differentiated carcinomas which have the best, poorly differentiated neoplasms the poorest, and medullary carcinomas with an intermediate prognosis. In well differentiated thyroid cancers (about 80% of all thyroid neoplasms) age is the most important factor in prognosis.⁴ It plays a more important role than does the extent or stage of the disease. In view of the

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striking influence of age on survivorship, critical examination of the unique biologic characteristics of thyroid neoplasms occurring in childhood and adolescence was undertaken.

Carcinoma of the thyroid is an unusual cause of death during childhood. Between the years 1958-67 in the United States, there were 60 deaths in children, accounting for 0.58% of all deaths from thyroid cancer.¹⁸ Most of the deaths occurred in patients with undifferentiated neoplasms. Although thyroid neoplasms are less common in children than adults, during the past 25 years an increased frequency in children has been noted. This is probably due to exposure of the thyroid to ionizing irradiation incident to treatment of hypertrophic nasopharyngeal lymphoid tissue and enlargement of the thymus, a practice which prevailed during the years 1920-1955.^{5,7,11,18,19}

The purpose of this paper is to review our experience with thyroid neoplasms in patients younger than 21 years of age.

Materials and Methods

Thyroid cancer registries are functioning at the North Carolina Memorial and University of Iowa Hospitals. Five hundred seventy-one patients with thyroid malignancies seen at both hospitals between 1930-74 have been assessed. There were two study groups: 58 patients younger than 21 years old at the time of diagnosis; 515 patients older than 21 years at diagnosis. Historical information, physical, laboratory, x-ray, pathological and surgical findings, treatment and other pertinent information were collected, recorded, coded, and stored in a computer. Annual followup information was obtained for all surviving patients either when the patients returned to

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Age Of Patients

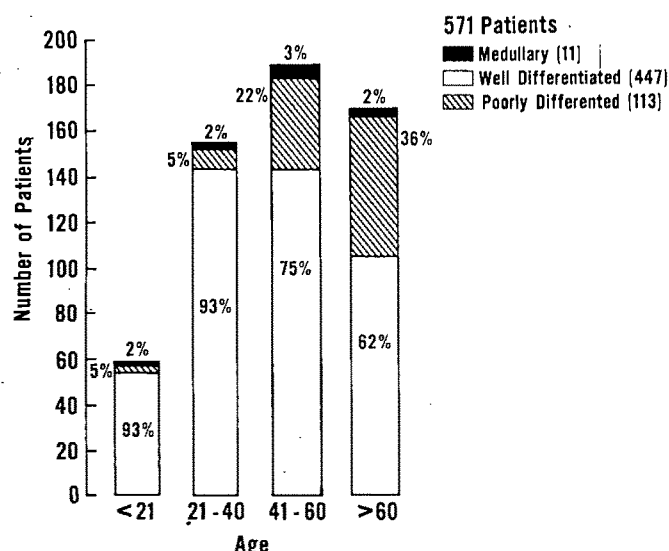


FIG. 1. Histologic classification of malignant thyroid neoplasms occurring in 571 patients.

the hospitals, by correspondence with patients and their physicians or from death certificates. The patient data was continuously updated as followup information was received. Computer programs were developed for analyzing the data. Survival rates were computed by a modification of the method described by Berkson and Gage.^{3,13}

The neoplasms were classified on the basis of the *pre-dominant* histologic pattern. The clinical pathologic stage of the neoplasm at the time of diagnosis was determined by clinical, surgical and pathological findings. Stage I included neoplasms limited to the thyroid gland; Stage II, extension to regional lymph nodes, and Stage III, extension beyond the regional lymph nodes.

Definitive surgical therapy consisted of 1) partial thyroidectomy (partial resection of one or both lobes), 2) lobectomy (resection of the lobe containing primary lesion with or without the isthmus), and 3) near total to total thyroidectomy. Near total thyroidectomy involved complete excision of the lobe containing the primary lesion and near total excision of the contralateral lobe leaving one to two grams of thyroid posteriorly in relationship to the branches of the inferior thyroid artery and parathyroid glands. Cancer metastatic to regional lymph nodes was removed by radical neck dissection (*en bloc* excision of the sternocleidomastoid muscle, jugular vein, the jugular, anterior and posterior cervical triangle lymph nodes) or partial neck dissection (excision of nodes from the central lower one third of the neck). In recent years most neck dissections have been performed with preservation of the sternocleidomastoid muscle and at least one internal jugular vein.

Results

The data shown (Fig. 1) indicate that, in younger people, well differentiated neoplasms of the thyroid occur more often, and poorly differentiated less often. There is no evidence that age affects prognosis in patients with medullary carcinomas or poorly differentiated neoplasms.¹⁷ Therefore, patients with these neoplasms are not included in the subsequent analyses and the discussion. The failure to recognize the significant difference in prognosis of well, poorly differentiated and medullary thyroid neoplasms detracts from the meaning and value of other studies.^{14,20}

In Fig. 2 are shown the number of patients with well differentiated thyroid carcinoma by the year of diagnosis (1940-1974). Most of the younger patients had the diagnosis established between 1950 and 1970. This appears to reflect a latent period of approximately 15 years between radiation exposure and the clinical diagnosis of thyroid cancer.

In Fig. 3 are shown the findings indicating the number of patients with papillary, follicular, and papillary-follicular lesions. In the latter patients the microscopic findings showed an approximately equal mixture of papillary and follicular histology. This highest incidence of follicular carcinoma occurred in the patients younger than 21 and in those older than 40 years.

Data related to size of the primary lesion was available for 336 of the 447 patients with well differentiated carcinomas. Lesions of three sizes were compared. (Fig. 4) Lesions larger than 4.0 cm in diameter were more com-

Year Of Diagnosis

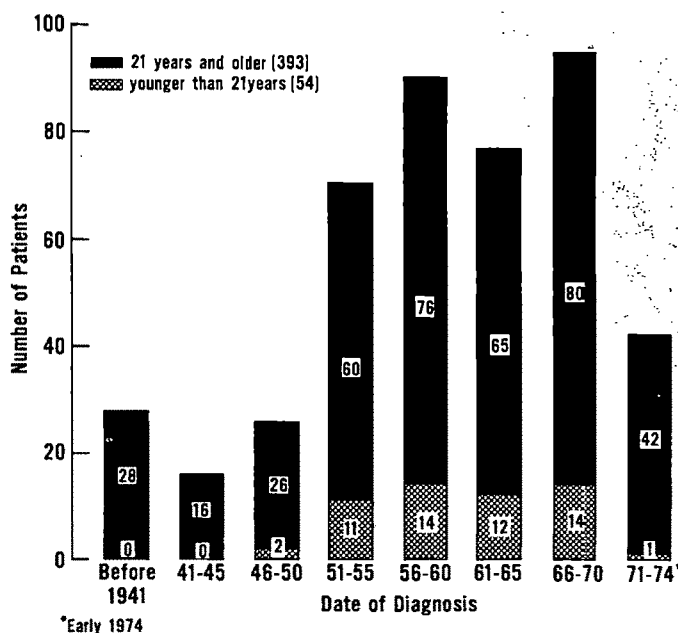


FIG. 2. Well differentiated thyroid carcinoma occurring in 447 patients according to the year in which the diagnosis was established.

Age Of Patients

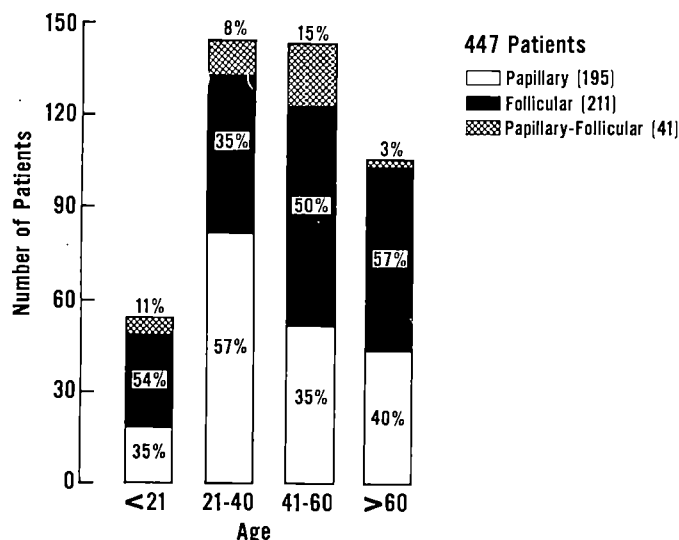


FIG. 3. Histologic type of 447 well differentiated thyroid carcinoma according to the age of the patients.

mon in patients 21 years and older. Slightly more than one third of childhood lesions measured between 2.5 and 4.0 cm in diameter. This size lesion was more common in younger than in older patients. Lesions less than 2.5 cm had approximately the same incidence in both age groups.

Although the primary neoplasm was more likely to be smaller, thyroid carcinomas were at a more advanced

Size Of Primary Lesion

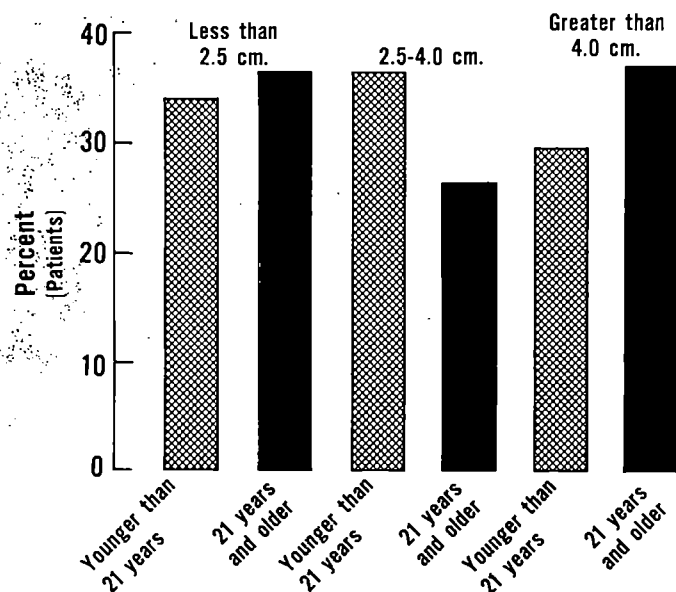


FIG. 4. Size of primary lesion of well differentiated thyroid carcinoma in patients younger than and 21 years and older.

Stage Of Disease

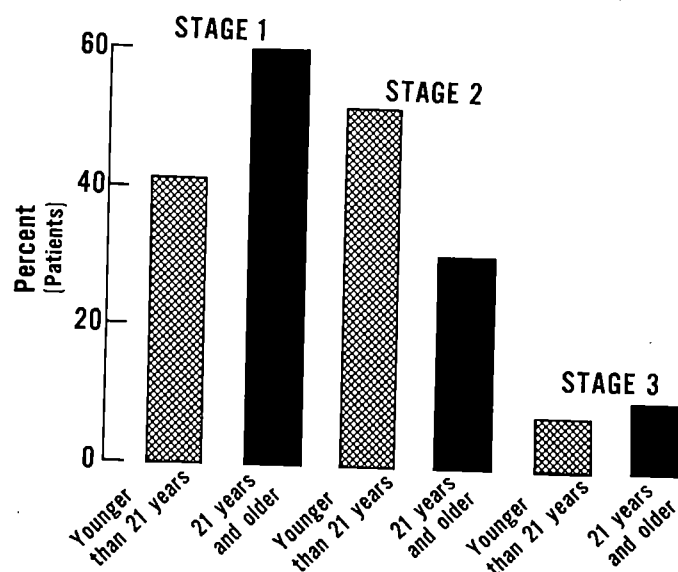


FIG. 5. Stage of disease of well differentiated thyroid carcinoma in patients younger than and 21 years and older.

clinical pathological stage in the younger patients (Fig. 5). Almost 60% of the younger patients had extension to lymph nodes or beyond compared with 41% of the older patients. Paradoxically, survival was significantly better in younger patients (53 of 54 or 98.1%) compared with that noted in the older patients (240 of 393 or 61.3%).

Well differentiated thyroid carcinoma occurred at least twice as often in females as males, irrespective of age;

Sex

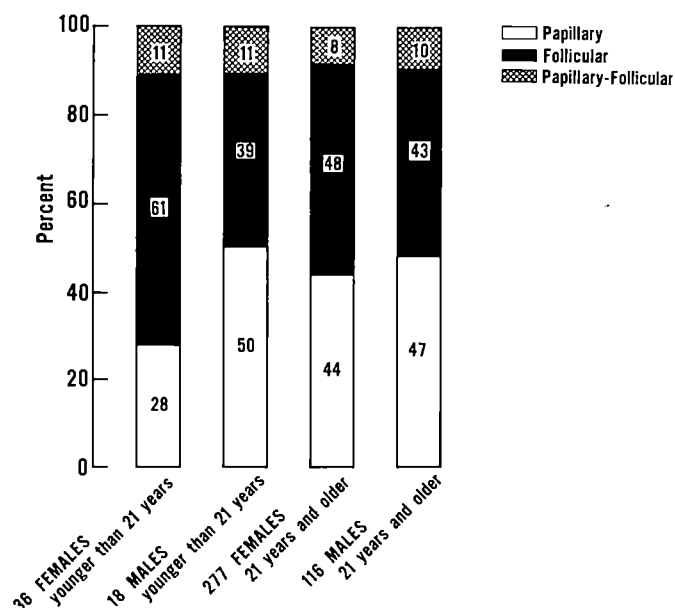


FIG. 6. Sex of patients by histologic classification of patients with well differentiated thyroid carcinoma younger than and 21 years and older.

TABLE 1. *Surgical Treatment of 447 Patients With Well Differentiated Thyroid Carcinoma.*

	54 Patients <21 Yrs		393 Patients >20 Yrs	
	No.	%	No.	%
Partial Thyroidectomy	12	22.2	74	18.8
Lobectomy	15	27.8	136	34.9
Near Total Thyroidectomy	27	50.0	140	35.6
No Surgical Treatment			41	10.7
Partial Neck Dissection	7	12.9	34	8.6
Radical Neck Dissection	21	38.9	78*	19.8

*Two patients had neck dissections without thyroid operations.

this higher incidence in females was more pronounced in the older patients (Fig. 6). Females were more likely to have follicular carcinoma than males. This predilection is greater in the younger patients. Conversely, the incidence of papillary carcinoma is higher in males than females, especially in patients younger than 21 years.

The types of surgical therapy are shown in (Table 1). The most striking finding is that 41 (10.7%) of the patients in the older age group were treated with no definitive operation. The relatively large number of near total thyroidectomies (50% vs. 35.6% in the older group) and neck dissections (51.8% vs. 28.4%) done in the younger patients is consistent with the increased incidence of Stage II lesions in this group (51.9% vs. 30.3%) and more aggressive surgical treatment.

Five of the 54 (9.3%) younger patients had *residual neoplasm* compared with 61 of the 351 (16.1%) older patients at the end of the definitive surgical operation. (Table 2) This is unexpected in view of the more advanced stage of the disease at the time of the diagnosis in the younger patients. Four of the younger patients (7.4%) developed recurrences following definitive surgical treatment compared with 52 (12.8%) of the older patients (Table 2). These findings are consistent with a more

aggressive surgical philosophy applied in the younger patients. This is documented by the findings recorded (Table 1). The numbers of younger patients in each of the 9 surgical therapy groups are too small to make meaningful comparisons.

The numbers of patients who developed permanent hypoparathyroidism, permanent vocal cord paresis and other complications following operation are indicated in Table 3. Other complications consisted of temporary hypoparathyroidism, temporary vocal cord paresis, tracheal obstruction requiring tracheostomy, wound hematoma and infection. Despite a more radical surgical approach, the incidence of postoperative complications did not differ significantly between the younger and older patients. The most important finding is that about 25% of the patients treated by total or near total thyroidectomy developed permanent hypoparathyroidism. The highest incidence occurred when a radical neck dissection was added to a near total thyroidectomy. Recurrent nerve injuries and other complications were also noted most frequently in patients who had a near total thyroidectomy and neck dissection. In contrast is the impressive absence of postoperative complications in patients treated by lobectomy.

Patients younger than 21 years of age have been followed for an average of 11 years, with a median followup time of 10 years; longest survival, 24 years. One male patient (1.2%) with papillary carcinoma is dead. The cause of death was undetermined. The patient had residual cancer at time of his demise. Patients 21 years and older at the time of diagnosis have been followed for an average of 14 years with a median of 13.5 years; 153 (38.7%) are dead.

Twelve (22.2%) of the younger and 21 (5.3%) of the older patients had irradiation treatment to the head and/or neck during infancy; the difference is statistically significant ($P < 0.02$).

TABLE 2. *Residual and Recurrent Neoplasm Observed in 447 Patients With Well Differentiated Thyroid Carcinoma.*

	No.	<21 Yrs.				No.	>20 Yrs.			
		No.	Residual %	No.	Recurrence %		No.	Residual %	No.	Recurrence %
Partial Thyroidectomy										
No Neck Dissect	10	1	10.0	1	10.0	62	17	27.4	13	21.0
Partial Neck Dissect	2	1	50.0	—	—	8	1	12.5	4	50.0
Radical Neck Dissect	0	—	—	—	—	4	2	50.0	0	0
Lobectomy										
No Neck Dissect	11	1	9.9	1	9.9	108	7	6.5	14	6.5
Partial Neck Dissect	1	—	—	1	9.9	10	1	10.0	0	0
Radical Neck Dissect	3	—	—	—	—	18	1	5.6	2	11.1
Near Total Thyroidectomy										
No Neck Dissect	5	1	20.0	—	—	70	19	27.1	11	15.7
Partial Neck Dissect	4	1	25.0	—	—	16	5	31.3	0	0
Radical Neck Dissect	18	—	—	1	5.6	54	8	14.8	8	14.8
Total	54	5	9.3	4	7.4	350	61	16.2	52	12.8

TABLE 3. Postoperative Complications Observed in 447 Patients With Well Differentiated Thyroid Carcinoma.

	<21	>20	Permanent Hypoparathyroidism				Permanent Cord Paresis				Other*			
			<21 Years		>20 Years		<21 Years		>20 Years		<21 Years		>20 Years	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Partial Thyroidectomy														
No Neck Dissect	10	62	—		0	0	—		5	8.1	2	20.0	12	19.4
Partial Neck Dissect	2	8	—		0	0	—		1	12.5	1	50.0	0	0
Radical Neck Dissect	0	4	—		0	0	—		0	0	—		2	50.0
Lobectomy														
No Neck Dissect	11	108	—		0	0	—		3	2.8	—		11	10.2
Partial Neck Dissect	1	10	—		0	0	—		0	0	—		0	0
Radical Neck Dissect	3	18	—		0	0	—		4	22.2	—		6	33.3
Near Total Thyroidectomy														
No Neck Dissect	5	70	1	20.0	7	10.0	—		11	17.1	—		17	24.3
Partial Neck Dissect	4	16	1	25.0	4	25.0	—		3	18.8	2	50.0	3	18.8
Radical Neck Dissect	18	54	5	27.8	11	20.0	3	16.7	5	10.9	14*	27.8	32	58.2

*Two or more complications occurred in some patients.

Discussion

The most striking finding of this study is the excellent prognosis associated with well differentiated thyroid carcinomas in young people. The life expectancy of a person younger than 21 years at the time of diagnosis of well differentiated thyroid cancer is the same as that of the normal population (Fig. 7). Our findings indicate that normal life expectancy of female patients with well differentiated carcinoma persists up to 40 years of age. Between 30 and 40 years of age, the survivorship of male patients begins to fall.⁴ When female and male patient

data are combined, because there are twice as many women as men, there is no evident drop off in survivorship during this decade (Fig. 7).

The reasons for the difference in the biologic behavior reflected by the differing prognosis of thyroid cancers in these two age groups, are not apparent. Paradoxically, as has been indicated (Fig. 5), the clinical pathologic stage of the disease was more advanced at the time of diagnosis in the younger than older patients. No differences in the gross or microscopic pathology of the carcinomas occurring in younger and older patients have been observed. The finding of the highest incidence of follicular carcinoma, but the lowest incidence of papillary carcinoma in females younger than 21 years, is interesting. There was evidence that, in adults, follicular carcinoma has a poorer prognosis than the papillary variety of well differentiated thyroid carcinoma.^{2,4} Progression of the well to poorly differentiated neoplasms occurring in the older patients was a factor possibly contributing to the poorer survivorship. This has been observed by us and documented by others.¹⁶ Post mortem examinations performed upon adults who have died as a result of their well differentiated neoplasms suggests that progression to poorly differentiated carcinoma occurs in less than 10% of these tumors. This has been rarely observed or reported in patients younger than 21 years old at the time of diagnosis.

Another important factor may be that the thyroid gland during infancy and childhood is more susceptible to carcinogenic stimuli. This may relate to the more active growth of the thyroid which is determined predominantly by thyrotrophic hormone (TSH). TSH may play a more prominent role as a promoting factor in younger patients. As a consequence, these neoplasms may be relatively, more TSH (hormone) dependent than those in the adult. Thus, TSH suppression could contribute to the better survivorship observed in young individuals. There is also evidence that some of these carcinomas are responsive to

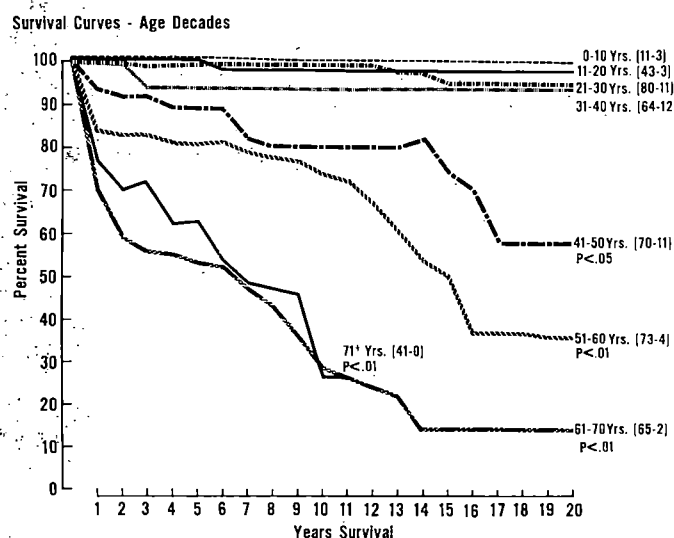


FIG. 7. The survival curves for patients with well differentiated thyroid carcinoma show the differences from the expected survival of normal individuals with the same sex distribution for each decade. The survivorship of the normal population is expressed as 100% for 20 years. For example, for patients who were 51-60 years old at diagnosis, there was a difference of 62% from the normal (expected) survival at 20 years, $P < .01$. The numbers in the parenthesis indicate how many patients there were of each decade and the number alive 20 years from the time of diagnosis.

inappropriate trophic hormones *e.g.* luteinizing hormone.¹² The rise in luteinizing hormone known to occur with menopause could be a factor in the poorer prognosis of thyroid cancer in females after the age of 40.

The higher incidence of irradiation to the head and neck during infancy noted in the younger patients is consistent with the concept that the thyroid epithelial cells are more sensitive to carcinogens early in life. Survival of these patients similar to the normal population, suggests that "irradiation induced carcinomas" behave no differently than the well differentiated carcinomas arising (*de novo*) in children. Electron microscopy and other more sophisticated techniques may demonstrate differences from adult carcinomas which are not evident using currently available histological methods.

There are no controlled studies on nonsurgical treatment. Therefore, it is possible that less aggressive treatment, *e.g.* hormone suppression or more limited surgery, might produce the same results as the management used in these patients. However, if the incidence of recurrence is considered, the aggressive surgical therapy which has been used would seem justified. Recurrent disease occurred despite suppression treatment. It was lowest (1 of 23 or 4%) in those patients with more extensive disease who had more radical operations. Patients treated by a partial thyroidectomy or lobectomy with or without neck dissection had a recurrence rate of three of 27 (11%).

The principal criticism of near total thyroidectomy is the high incidence of permanent hypoparathyroidism (7 of 23 or 26% of patients). Although significant, the lifetime morbidity of permanent hypoparathyroidism can be controlled with appropriate medication with no apparent long term ill effects. Sectioning and reimplantation of parathyroids may possibly result in adequate parathyroid function.¹ We have had limited experience with parathyroid implantation. We have seen hypoparathyroidism develop in spite of preservation of parathyroid glands. Interference with their tenuous blood supply is the probable explanation.

Following the initial observations of Dunhill in 1937⁸ confirmed by Crile in 1957⁶ and Thomas in 1957¹⁵ virtually all patients with thyroid cancer have been placed upon suppressive doses of thyroid hormone. This is done for two reasons: 1) To insure euthyroidism regardless of the amount of normal thyroid parenchyma remaining, and 2) to provide maximum suppression of TSH which may play a role as a promoting factor in thyroid cancer. This approach has particular implications to children. Thyroid hormone is given in the form of desiccated thyroid 180 mgms, thyroxin 0.3 mg or triiodothyronine 75-125 mcg. This amount of thyroid hormone is excessive compared to physiologic level of thyroid hormone indicated by the dosage of thyroid hormone required to suppress TSH to normal levels in patients with hypothyroidism. We have no evidence that these "phar-

macologic" doses retard the growth and development of these children.

The role of TSH as a promoting factor in the development of thyroid cancer in experimental animal has been well documented. There is evidence that similar mechanisms are operative in man. The role of TSH suppression as a factor in survivorship and a deterrent to recurrent disease has been difficult to evaluate because of the lack of controlled observations. On theoretical grounds, however, (*vide supra*) suppression of TSH is a logical adjuvant to surgical treatment. It is of interest that in no patients (5 with residual disease and 4 with recurrence) was there evidence of progression to a more undifferentiated neoplasm. The evidence that TSH may be elevated in patients with thyroid cancer and that this is not as readily suppressed by conventional doses of thyroid hormone is inconclusive.⁹ Although we have no preoperative values in this particular age group, our data suggest that TSH does not remain elevated despite maximum doses of thyroid hormone.

The adequacy of TSH suppression in the past has been determined indirectly by measuring fall in ¹³¹I uptake and fall in serum thyroxine when patient is taking 1-triiodothyronine. The ability to measure TSH by radio immunoassay provides a direct method of measuring the effectiveness of suppressive treatment with thyroid hormone. Normal TSH levels measure between 1 and 10 U/ml. The failure of TSH to fall below preoperative values and to a subnormal range suggests inadequate dosage of thyroid hormone. These measurements would seem particularly appropriate in these patients known to have residual or recurrent disease.

Fifteen of the younger and 64 of the older patients have been treated with ¹³¹I for residual or recurrent neoplasm. We are unable to attribute to radio iodine therapy the significant benefits which have been described by others.^{10,14}

Acknowledgment

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DISCUSSION

DR. R. B. WELBOURN (London, England): I am particularly pleased to discuss briefly this paper by Dr. Thomas and his colleagues, because Dr. Joe Buckwalter worked at Hammersmoth in the time of my predecessor, Ian Aird. My own experience of this problem is not great, but I am very interested in it. I have no new observations to report, but would like to ask three questions.

First, the data shows clearly that younger patients fared better than the older ones, and this agrees with the experience of others. Because the disease was more extensive in the younger ones, they received more aggressive surgical therapy. There are, therefore, two variables, namely age and extent of operation, and it seems to me impossible from these data to establish which was responsible for the better prognosis. Can Dr. Thomas help us?

Secondly, it is of interest that more than half the patients had follicular lesions. In the series of over 500 children from all over the world, reported by Winship and Rosvoll in 1961, nearly 80% of the differentiated lesions were *papillary*, not follicular. In this large series about 80% had received radiotherapy to the neck previously and this was presumably an etiological factor. Irradiation usually causes papillary lesions. It is surprising that there were more follicular lesions in Dr. Thomas' series. Has he any explanation?

Thirdly, Dr. Thomas used surgical operations together with thyroid hormonal therapy. This latter, which was introduced by Sir Thomas Dunhill in London in 1937, is usually most effective in papillary lesions. Are we to assume from Dr. Thomas' data that it is also highly effective against follicular growths in children?

DR. CHARLES ECKERT (Albany, New York): I have long been interested in the question of thyroid cancer, and have a few observations to make with regard to this excellent paper by Dr. Thomas and his coworkers, from Iowa and North Carolina.

I must first say that our own experience with carcinoma of the thyroid in childhood is similar to the data reported by Dr. Welbourn except that most of our patients have had either papillary or mixed papillary and follicular cancers, with only a small number of pure follicular cancers of the thyroid, (in the childhood age group).

I must also say that, unfortunately, we don't have as large a series of cancer of the thyroid in children as that reported from these two institutions. However, over the years we have seen approximately 35 such patients, dating back to the late 1940s. Four of these patients I have operated on with bilateral disease, necessitating bilateral neck dissection, have survived without further evidence of difficulty up to the present time; and I continue to have personal followup with these four patients.

The other patients have done well, with two exceptions. Both patients were operated upon by Dr. John McClintock at Albany. As many of you know, McClintock almost confined his work to diseases of the thyroid and amassed a very large experience. One of his patients had follicular cancer which directly invaded the jugular vein. Unfortunately, I didn't bring the slide that illustrates that, because it's rather unique. The other patient had papillary cancer, and died as a result of metastatic

disease. Although death from thyroid cancer is infrequent in the first two decades of life it does occur.

Some years ago we described a relatively radical operation for treating papillary cancer of the thyroid in adults as well as children. It included preservation of the sternocleidomastoid muscle but is otherwise a typical radical neck dissection. The operation has been modified in various ways over the years, but it still is an attempt to radically remove lymph nodes. I must tell you that I have been unable to demonstrate that, in children, there is any correlation between the degree of radicalness of the operation and the end results.

Unfortunately, as far as I can tell from the data presented by Dr. Thomas and his group, while the patients have done well, most of them have been treated by relatively radical means. Without a control group it is impossible to attribute the good results to the type of operation used in treatment. We do know from other reports, however, that "berry-picking operations" are attended by very good survival data. Years ago, in my St. Louis days, we were unable to correlate the type of operation with the end results. The uniformly good results are apparently due to the biologic nature of the host-disease interaction, rather than what we do surgically. I wish I could say otherwise.

DR. JOHN L. SAWYERS (Nashville, Tennessee): Drs. Louis Rosenfeld and Ed Withers, from the Department of Surgery at Vanderbilt University, have just reviewed our experience with thyroid cancer. While the experience is not as large as Drs. Thomas, Buckwalter and Freeman, it does parallel their results, but with a few differences.

(Slide) There were 21 childhood cancers in 184 patients, or roughly 10%. Most were females. All were white. And the important thing, as Dr. Thomas pointed out, is to follow these patients. All our patients have a 100% followup.

(Slide) Unlike his series, we found that 71% of the patients had papillary adenocarcinoma, and one of these died. There were 29% follicular adenocarcinomas with two deaths, one at eight years and one at 20 years. So we would agree with Dr. Thomas that age at the time of diagnosis is a very important factor in prognosis. But some children do die of thyroid cancer.

Seventy-five per cent of these cancers presented with a solitary nodule. Drs. Patton and Hollifield from Vanderbilt University have recently described a new scan which appears to be more accurate than the usual radioactive thyroid scan in evaluating thyroid nodules. This is the americium 241 scan, which is a modification of Hoffer's fluorescent technique.

(Slide) The top part of the slide shows the usual thyroid emission scan using radioactive iodine, and there's a cold nodule at this location. (Indicating) Even though the incidence of carcinoma is greater in cold, as compared to hot nodules, up to 90% of cold nodules may be benign, and there is a need for an improved, noninvasive technique to separate malignant cold nodules from the heterogeneous group of cold nodules which are benign.

This americium²⁴¹ scan, shown on the lower half of the slide, appears to do this. The electrons around the iodine stem are excited by the americium, so that the scan measures the *energy* of electrons as they fall back into their shells after being excited. The technique precisely quantifies total thyroid iodine.

Its advantages are: 1) nothing is injected; 2) the scan is not affected by exogenous iodine; and 3) there is no waiting period for results. The ratio of the nodular iodine (N) to other iodine (T) of 0.6 or less is suggestive of a malignant nodule. In the thirty-nine patients examined by this technique all malignant nodules lay below the 0.6 ratio line.

There have been only four false positives; and, of even more importance, there have been no false negatives.

DR. JOSEPH A. BUCKWALTER (Closing discussion): As indicated by Dr. Thomas, relatively more total thyroidectomies and neck dissections have been done in the young patient group. However, this indication of "more radical" surgery in the younger patients does not provide an adequate explanation for the strikingly better prognosis related to age.

The three discussants referred to the problem of classification. As indicated, our classification of well differentiated thyroid carcinoma is on the basis of the predominant histologic pattern. If a sufficient number of sections of the primary lesion in the thyroid and the metastases are obtained, in most patients with well differentiated carcinoma both follicular and papillary patterns will be found. More commonly, any well differentiated thyroid carcinoma is classified as papillary if this pattern is found in any section even though it may not predominate.

We have found no evidence of a difference in response of follicular and papillary neoplasms to thyroid hormone suppressive therapy. It is of interest that one of the first cases treated and reported by Dunhill was a child.

I would like to show two slides. The first is an expansion of the slide which Dr. Thomas showed, indicating that during the first four decades, patients have a survival comparable to the normal population. Note that in patients in which the diagnosis is established after 40 years of age there is substantial dropoff in survival from the expected. The survival curves are computed on the basis of an expected survival of the normal population expressed as 100% for 20 years. Thus in the fifth decade group of patients at 20 years there is a 40% reduction in survival compared with the normal population. The data recorded in the figure indicate that there is a direct relationship between the fall in the survival and aging of the patients.

Dr. Thomas indicated that we are unable to find any association of sex to survival in children. (Slide) These findings which have been previously reported show that women younger than 40 at the age of diagnosis have a survival similar to the normal population compared with men in the same age group who have a significant reduction their survival. In patients older than 40 years of age at diagnosis the survivorship of women is poorer than in the younger age group, but is much better than that of men. The association of age to survivorship, however, is much stronger than sex.

It is important to reiterate that it is possible that the younger patients, the mean followup is about 15 years, when they reach 40 years of age may develop the same survivorship pattern that we have reported in the older age patients.

Aortic and Other Arterial Injuries

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WILLIAM A. NEELY, M.D., F.A.C.S., DON W. BERRY, M.D.

Three hundred sixty arterial injuries in 353 patients are reviewed. They covered a wide spectrum of injuries and included 36 aortic injuries and 19 cases of carotid trauma. The mortality rate of 12% was in large part due to aortic injuries. Shock was the predominant cause of death. Infection was the most frequent non-fatal complication. Pulmonary complications were surprisingly uncommon. With methods and techniques discussed in the paper, 90% satisfactory end results were achieved. The amputation rate was 6% where extremity injuries were involved.

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THE PRIMARY RECONSTRUCTIVE repair of arterial injuries has become firmly established in surgical practice in this country ever since the Korean conflict. Moreover, the management of arterial trauma is usually a rewarding exercise for the vascular surgeon since the patients are often young, heal well with few complications, and the technique is frequently challenging. Nevertheless, if minimal morbidity and mortality are to be expected, there must be meticulous deference to certain principles unique to this type of surgery. In addition, exclusive clinical features and complications along with the special management techniques required to deal with them have helped to accord clinical distinctiveness to arterial trauma in surgical practice. We propose to review some aspects of this discipline in the light of our own experience with 353 patients and to delineate our approach to certain problems, the solution of which remains controversial. Illustrative case reports will be cited when appropriate.

Clinical Material

Three hundred sixty arterial injuries in 353 patients were treated in the University of Mississippi Hospital between 1957 and mid 1974. The anatomic distribution and mechanism of injury are shown in Tables 1 and 2 respectively and in Figures 1 and 2. The extremities were involved in roughly two-thirds of the cases (60%). As might be expected, stab injuries were more frequent in the upper limb (39 cases) than in the lower limb vascula-

ture (14 cases). Blunt trauma was the cause of injury in 48 cases, more than three-fourths of which were associated with bone fracture or joint dislocation. Of special interest were 20 cases of iatrogenic arterial injury which included mechanisms as ubiquitous as brachial artery injury from cardiac catheterization, as well as uncommon types such as common iliac arteriovenous fistula following intervertebral disc surgery, femoral artery dissection due to sharp instrumentation during total hip replacement, and internal mammary arteriovenous fistula following attempted subclavian venipuncture. Fifty-one per cent of the patient population reviewed was 30 years or younger in age. The distribution of 36 aortic injuries and 19 carotid vascular injuries are depicted in Figures 4 and 7 respectively. There were 19 popliteal artery injuries which represented 5% of the total cases treated. Thirty-seven of the firearm injuries treated were shotgun injuries. The incidence of arteriovenous fistulae was 10% (38 cases). The aforementioned groups will be treated in greater detail, due to the special problems associated with their management.

Types of Arterial Injuries

The types of arterial injury inflicted and associated injuries are listed in Tables 4 and 6 respectively and in Figure 3. Unusual but not uncommon types of injury included 2 instances of arterial spasm without thrombosis, 3 cases of true arterial aneurysms due to weakening of the vessel wall by blunt trauma, and 5 cases of missile embolism (Table 5). It will be noted that major veins were involved in approximately one-fifth of the cases, 50% of which developed into arteriovenous fistulae. Roughly the same number of gastrointestinal injuries, bone fractures, and neurological injuries occurred.

Manifestations of Arterial Injuries

Presenting clinical features of the case material are shown in Table 3. Nearly one-fourth of all cases pre-

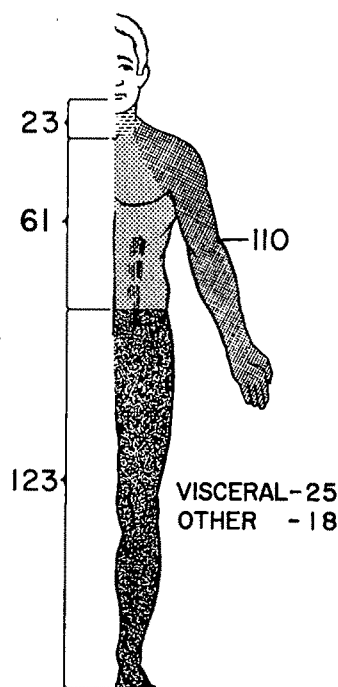


FIG. 1. Anatomic distribution of 360 arterial injuries.

sented in shock. Of special interest, local hematoma or other evidence of external hemorrhage was present in initial clinical examination in only 31% of all involved injuries. Among vascular injuries of the upper and lower extremities, 25% presented with color or temperature change, 47% with absent distal pulse, 11% with decreased distal pulses but approximately 20% of the cases had good distal pulses in spite of major arterial injury.

Considering the absence of striking physical signs and the presence of misleading ones in some cases, it is not surprising that arteriography was necessary to establish a more precise diagnosis. This was done in 168 instances (52% of the total cases).

Some uncommon manifestations of arterial injury included subclavian steal due to missile obstruction of the first part of the left subclavian artery, transient cerebral ischemia and coma due to carotid injury, and bullet embolism.

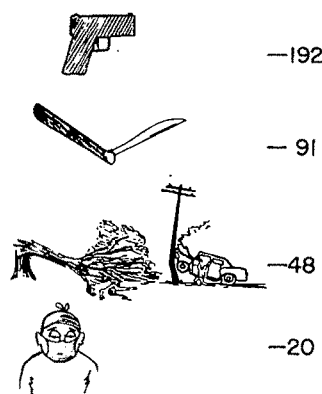


FIG. 2. Mechanisms of arterial injury in 353 patients. Not shown are 9 injuries due to miscellaneous or undetermined causes.

TABLE 1. Distribution of 360 Aortic and Arterial Injuries in 353 Patients
No. of Cases

Aortic		
Thoracic		14
Abdominal		22
Upper Limb		
Axillary and Branches		23
Brachial and Branches		75
Lower Limb		
Femoral and Branches		84
Popliteal and Branches		32
Head, Neck and Base of Neck		
Carotid		19
Subclavian		12
Other		8
Chest (excluding the 14 aortic injuries)		27
Abdomen		
Non-visceral (excluding the 22 aortic injuries)		18
Visceral		26
Total:		360

Specific Arterial Injuries

Aortic Injuries

The anatomic distribution of 36 aortic injuries is shown in Figure 4. The majority of the cases were due to gunshot wounds, but included 7 cases of deceleration injury in motor vehicle accidents. Three patients with aortic injury were dead on arrival at the emergency room. Eleven others were moribund and died in surgery before repair could be achieved. In 22 patients arterial repair was effected, with fabric grafts being used in 5 instances. In the other 17 patients, aortic bleeding was controlled by lateral suture. Six of these patients who underwent satisfactory repair died in the postoperative period. The overall mortality rate in this group of injuries was 58%. Excluding those who died on the operating table, the mortality rate was still high at 35%. An analysis of the 7 patients who died postoperatively showed that two patients died due to shock, and in 5 others the mechanism of death was attributable to sepsis. Acute tubular necrosis was the overriding factor in 3 patients, and gastrointestinal bleeding occurred in 2. The high incidence of sepsis in this group of patients was not surprising, as all but two cases of abdominal aortic injury had coincidental gastrointestinal or pancreatic injury. Among the 15 sur-

TABLE 2. Method of Arterial Injury in 360 Cases

Firearms		
Gunshot	155	192
Shotgun	37	91
Stab Wounds and Lacerations		
Blunt Trauma		
Automobile	29	48
Other	19	20
Iatrogenic		9
Miscellaneous, unknown		
Total:		360

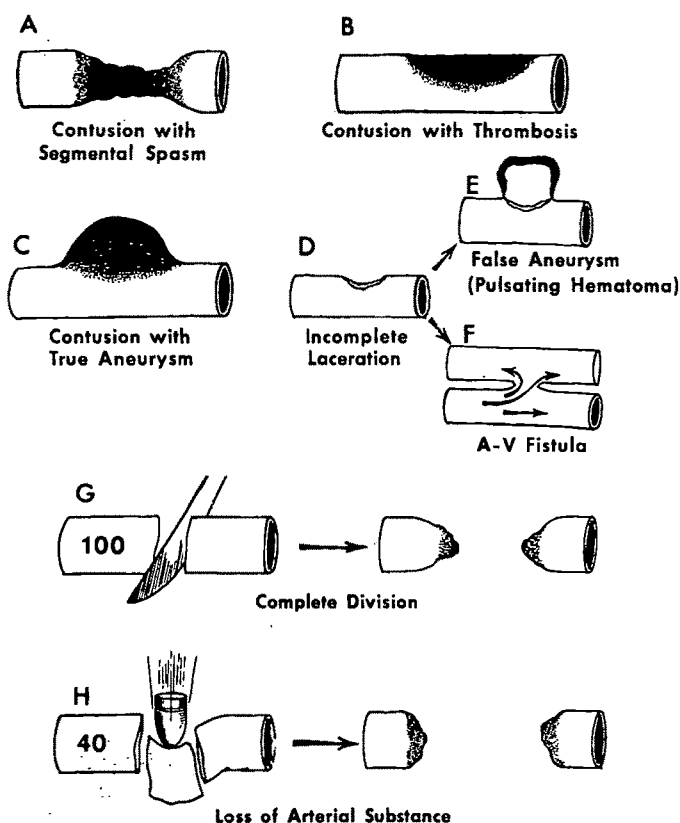


FIG. 3. Types of arterial injury.

vivors, 4 patients had serious complications; 2 had acute tubular necrosis which ultimately resolved, and 2 had bullet embolism. The overall incidence of acute tubular necrosis in this group of patients was therefore high (5 cases). In the two patients with missile embolism, the site of entry was the ascending aorta; surprisingly, both of these patients survived.

Traumatic Rupture of Aorta: The Widened Mediastinum Following Trauma. J.P.G., an 18-year-old male, was involved in a motor vehicle accident, when he was thrown against the dashboard. He was taken to a local hospital where he was carefully examined and found to have stable vital signs. He was fully conscious and was in

TABLE 3. 360 Arterial Injuries—Presenting Features*

	Percent Presenting
Absent Pulse	33% (47% ^a)
Decreased Pulse	8% (11% ^a)
Good Pulse despite arterial injury	13% (20% ^a)
Color or temperature change in extremity	17% (25% ^a)
Gangrene	> 1%
Shock	25%
Hematoma	19%
Hemorrhage	12%
Pulsatile mass or bruit	17%
Other	1%

*Some presented with more than one feature.

^aCalculated as % of extremity injuries only.

TABLE 4. 360 Arterial Injuries—Type of Injury

Type of Injury	No. of Cases
Laceration	111
Perforation, Transection and Loss of Arterial Substance	140
False Aneurysm	39
Arteriovenous Fistula	38
Contusion and Thrombosis	21
True Aneurysm	3
Vasospasm	2
Burn	1
Missile Embolism	5

mild discomfort. Physical examination revealed no obvious evidence of injury. However, chest roentgenogram revealed a widened upper mediastinum, and his local physician correctly made the diagnosis of ruptured aorta. He was rapidly transferred to the University Hospital via helicopter, where on arrival an aortogram showed a tear in the descending thoracic aorta just distal to the left subclavian artery. The patient's condition had continued to be stable, but he was rushed to surgery where he underwent a left thoractomy. Continuous bleeding was occurring through a small hole in the parietal pleura adjacent to the aorta. Partial cardiopulmonary bypass was instituted by cannulation of the femoral artery and a vena caval catheter introduced through the femoral vein. The aortic rupture was complete through all the layers of the aorta save for a thin layer of adventitia which had prevented exsanguination. The false aneurysm was successfully resected and aortic continuity restored by using a woven Dacron graft. The patient had an essentially uncomplicated postoperative course except for pulmonary atelectasis which resolved with the usual measures.

Comment. Since the clinical features of aortic rupture secondary to blunt trauma²² have become widely known, the necessity of aortography in suspected instances is now well recognized. Considering the nature of the aortic injury and the thin adventitial covering of the false aneurysm, it would seem preferable to perform aortography through the axillary artery rather than the femoral in retrograde fashion. However, in our experience, the retrograde technique has been generally safe. Others have suggested the so-called forward technique of arteriography by introducing the dye into the right at-

TABLE 5. 5 Cases of Missile Embolism.

Missile	Wound of Entry	Site of Lodgment
.22 Gunshot	Ascending aorta	Brachial
.22 Gunshot	Ascending aorta	Popliteal
Shotgun	Carotid	Middle cerebral
20 G Shotgun	Superficial femoral	Distal post tibial
.22 Gunshot	Atrium	Deep femoral

TABLE 6. Arterial Trauma—Major Associated Injuries In 360 Cases

Associated Injury	% Cases
Major Veins	21%
Gastrointestinal	20%
Other Abdominal Viscera	6%
Bone	17%
Nerves	17%
Muscle and Tendons	7%
Urinary Tract	4%
Lung	4%
Other	1%

rium.^{3,22} This technique generally results in poor quality arteriography and has not been found optimal in our experience. Excellent contrast delineation of the aorta is essential in this syndrome, since even the slightest intimal irregularity immediately beyond the left subclavian takeoff calls for prompt exploration. The aortic injury is often more extensive than suggested by aortography. Procrastination, because aortographic changes are minimal or because the patient is stable, can be disastrous as delayed rupture of the injured aorta is well recognized. Occasionally in some fortunate instances, an unrecognized aortic rupture will present with a false aneurysm after a lapse of a few years. Other diagnostic difficulties in traumatic rupture of the aorta include the

presence of a spuriously widened mediastinum, often seen in the anterior-posterior projections of a plain chest film, which is often the only projection available in a seriously injured patient. Occasionally aortic rupture may be present with a normal mediastinal contour on radiography. When aortic injury is suspected in a stable individual, it has been our policy to carry out expeditious aortography to better localize the site of injury.³ Elective surgical approach to the ascending and descending aorta varies. However, in a considerable proportion of our patients with aortic injury, especially secondary to penetrating trauma, preliminary diagnostic maneuvers were impossible, and expeditious surgery, sometimes in the emergency room itself, was called for as a lifesaving measure. Under such circumstances it is our policy to open the chest through a median sternotomy with the patient positioned at 45 degrees left lateral position. The incision can be extended into the left chest through the fifth intercostal space if access to the left ventricle, aortic arch, or descending aorta is required. Emergency cannulation for cardiopulmonary bypass is also possible with the patient in this position. As noted by others⁸ this approach is versatile but carries a higher morbidity than the regular median sternotomy or the standard left thoracotomy incisions. If injury to the descending aorta is established preoperatively, we employ a left thoracotomy incision. The question of whether or not to use a bypass during cross-clamping of the aorta remains in dispute, but we continue to use a bypass of one type or another.

Injury to Abdominal Aorta With Loss of Right Kidney: Temporary Perfusion of Left Kidney. W.G., a 23-year-old man, had been operated upon in another hospital for gunshot wounds of the abdomen. The patient had had multiple small bowel perforations which were closed and had undergone a colostomy for a colon injury. At that time a retroperitoneal hematoma had been noticed which was non-expanding and non-pulsatile and the surgeon had elected not to explore it. The patient had had a protracted hospital course during which time his colostomy had been closed and he had required two further operations for release of intra-abdominal lesions. He appeared to be doing well for awhile but felt ill and saw his local physician again. At this time a pulsatile abdominal mass was noted and the patient's blood pressure was recorded as 220/160 mm Hg. An intravenous pyelogram showed a non-functioning right kidney. At this time he was referred to the University Medical Center for further management. An arteriogram revealed a 12 cm false aneurysm of the aorta, a contracted right kidney fed by capsular and ureteric collaterals and non-visualization of the right renal artery. He was taken to surgery where the proximal clamp had to be applied above the left renal artery, which was supplying the only surviving good kidney of this patient. Dissection was difficult and the total aortic cross-clamping time approached two hours. During

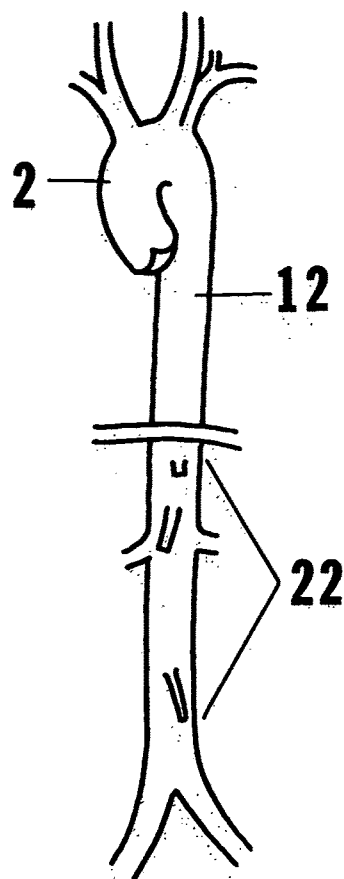


FIG. 4. Anatomical distribution of 36 aortic injuries.

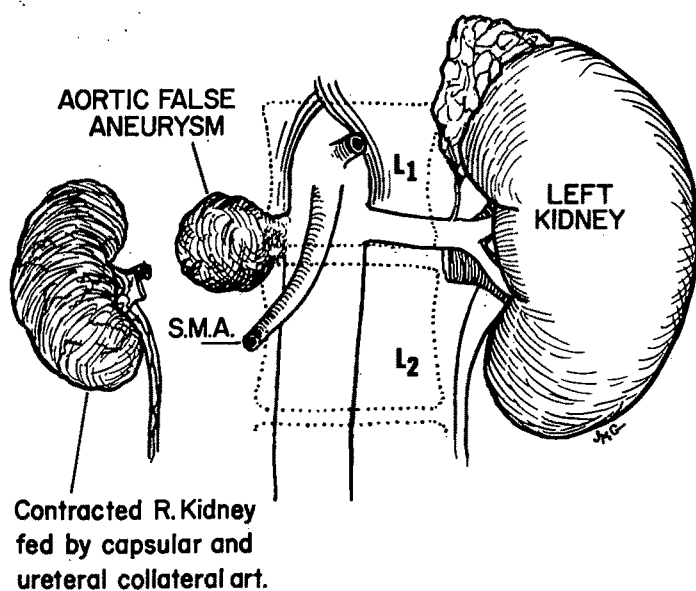


FIG. 5. Aortic false aneurysm resulting from gunshot wound. The right renal artery was almost completely destroyed.

this time the left renal artery was intermittently perfused with a cold solution for renal preservation. The right kidney was one-third the size of the left kidney, and it was decided to remove it since no usable part of the right renal artery was found for distal anastomosis. The method of repair with re-implantation of the left renal artery is shown in Figures 5 and 6. The patient had a benign postoperative course in the hospital and has been normotensive ever since.

Comment. It is possible that this patient would not have lost his other kidney if the retroperitoneal hematoma had been explored at the initial operation. In addition, he was subjected to the risk of a difficult and hazardous second procedure. From a technical standpoint, it is usually easier to repair an arterial injury immediately after its occurrence, before fibrosis renders dissection difficult.

The case also illustrates successful renal preservation of the patient's only remaining kidney despite a total aortic cross-clamping time of over two hours. With increasing experience and effective techniques for renal preservation during renal transplantation, it should rarely be necessary to carry out nephrectomy for major renal vascular injury. If satisfactory repair were not immediately possible, this could be done at leisure on the perfusion apparatus and the organ later re-implanted into the patient if optimal conditions obtained.

Carotid Injuries

The 19 carotid injuries that were seen are represented diagrammatically in Figure 7. These included three instances of carotid cavernous sinus fistulae secondary to

trauma. Three patients presented with contralateral hemiplegia, and 5 others with either shock or hemorrhage from the neck wound. In 3 other patients the presence of a bruit over the carotid led to the diagnosis of vascular injury. In the remaining 5 patients there were no specific symptoms or signs attributable to the carotid injury, but the diagnosis was made on the basis of arteriography or exploration. In all but 4 cases the mechanism of injury was a gunshot wound. There was one case each of stabbing, motor vehicle accident, iatrogenic cause due to arteriography, and a burn. The burn was third degree involving the head and neck; the trachea was almost completely destroyed and there was involvement of both carotids. Secondary bleeding from disruption of the right and left carotids occurred on the third and sixth post-burn days respectively. In each instance the carotid was debrided and replaced with a Teflon prosthesis. However, the patient did not survive his pulmonary complications secondary to tracheal destruction. All other patients survived reconstructive surgery.

Surprisingly, in 11 patients the carotid was the sole major cervical injury detected. In 8 other patients there was involvement of the internal jugular vein; in 3 instances, trachea; in 2 instances, cervical cord; and the cavernous sinus was involved 3 times.

Operative Technique

In 6 cases end-to-end repair was resorted to, and in 3 others lateral suture adequately restored continuity. Fabric grafts were used in 4 instances. However, we favor

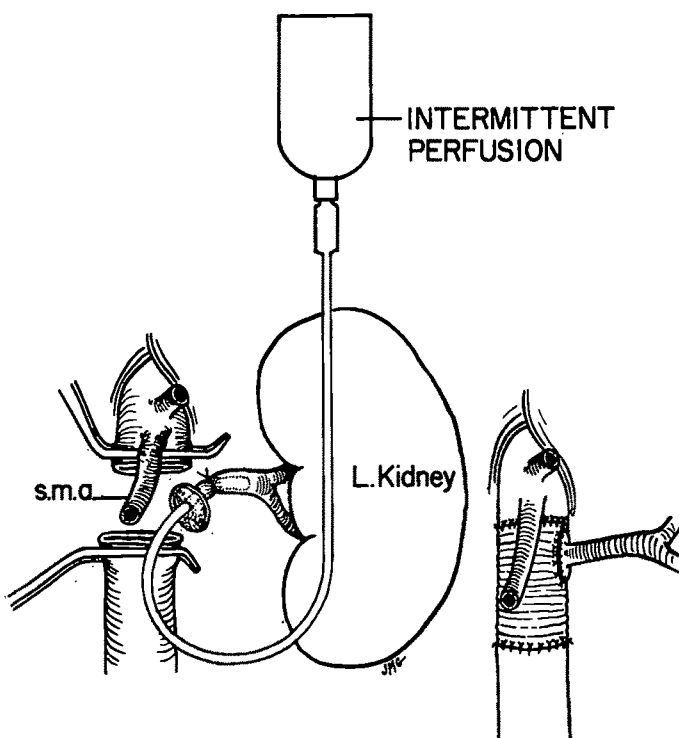
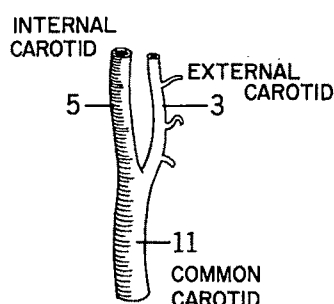


FIG. 6. Renal preservation in repair of aortic false aneurysm.

FIG. 7. Distribution of 19 carotid injuries.



saphenous vein graft now: recently we employed such a graft in a case of carotid injury, which is not included in this series due to the short followup period. Except for the 3 cases of arteriovenous fistulae and one case of false aneurysm, significant carotid flow through the injured artery was not noticed at the time of surgery. The total time of compromised perfusion (time of injury to repair) varied from a few hours to as long as 70 days. No temporary shunts were used during surgical repair except in one instance of carotid false aneurysm, with already established hemiplegia at the time of surgery. There were no postoperative neurological deficits attributable to the lack of an intraoperative shunt in any of our patients, although in one instance there was temporary loss of visual acuity for a short time probably due to a small embolus. The 3 patients with preoperative hemiplegia secondary to their carotid lesions all improved following reconstructive carotid surgery. In one patient the neurological improvement was dramatic and swift following surgery; this patient will be discussed subsequently. All 3 patients with internal carotid cavernous sinus fistulae underwent ligation of the internal carotid and ophthalmic arteries. In one instance muscle embolization was also used.

Problems Peculiar to Carotid Injuries

Carotid Injury With Hemiplegia: Restoration With Repair. E.P.S., a 62-year-old man was referred to the University Hospital 48 hours after receiving a stab wound to the right side of his neck. During emergency surgery by the referring physician a tracheostomy was done, and the common carotid injured by the stab was mass ligated. There was rapid progression of left hemiplegia following this procedure, and when seen in the emergency room at the University Hospital, the patient was moribund with Cheyne-Stokes respiration and hyperthermia (105°F). He was taken to surgery immediately where the mass sutures were removed, and stab wounds in the internal and common carotid arteries were repaired. The patient had considerable arteriosclerotic disease of the bifurcation and, therefore, an endarterectomy was carried out successfully. At the end of the procedure there was excellent backbleeding from both the external and internal carotids, and on removal of the clamps excellent pulsa-

tions in the internal carotid were present. Almost immediately after recovering from anesthesia, the patient started moving his left side which had previously been completely paralyzed. The neurological recovery was so rapid that by the next morning the patient was well oriented. He was discharged on the seventh postoperative day for further followup by his local physician.

Comment. The immediate problem in management of carotid artery injury is to maintain the airway despite the expanding cervical hematoma. A tracheostomy is undesirable as vascular surgery is probable. Every attempt should be made to intubate the patient, which may be very difficult due to deviation of the larynx and trachea by the hematoma. An experienced anesthesiologist is required. We have not found it necessary to carry out arteriography in the presence of an obvious arterial injury in the neck. Immediate exploration is indicated. There is little controversy regarding management of carotid injuries without neurological deficit;^{2,4,12} carotid repair is uniformly advocated. There is little enthusiasm for the use of intraoperative shunts in this group of patients. We have seldom used one. There is, however, controversy^{4,11,12,25} regarding the choice of treatment for a patient who has hemiplegia following carotid injury. In a great majority of these patients the injury is located in the internal carotid, compromising even the collateral flow from the external carotid. It has been feared that revascularization may lead to the development of a hemorrhagic infarct.²⁵ This seems to have been the experience of many^{11,25} but not all⁴ who have had experience in this area. As the above case shows, our own experience has been favorable. Reasons for discrepancies in experience are unclear. In some patients with complete clotting of the internal carotid system extending intracranially, it may be impossible to restore perfusion by this route. Fogarty catheterization of the internal carotid is not advocated for fear of distal lodgment of clots. At any rate, the catheter will not usually negotiate the carotid siphon. Our present approach to internal carotid injuries with thrombosis is to re-establish continuity only if the thrombus can be evacuated easily and good backbleeding is obtained. Otherwise, ligation is the treatment of choice. Ligation is advocated by many for all carotid injuries presenting with hemiplegia. For blunt trauma even a nonoperative approach has been proposed. Clearly, the ideal treatment for this difficult group of patients awaits further study and experience.

Some patients with serious carotid injury may initially present with no serious symptoms.⁷ On this basis the routine exploration of all neck wounds without the delay of arteriography is in practice in some centers.^{7,9} We and others²⁰ have approached this problem somewhat differently. All neck injuries with clinical evidence of major vascular or other injury are immediately explored. In other patients where the clinical picture is benign, we

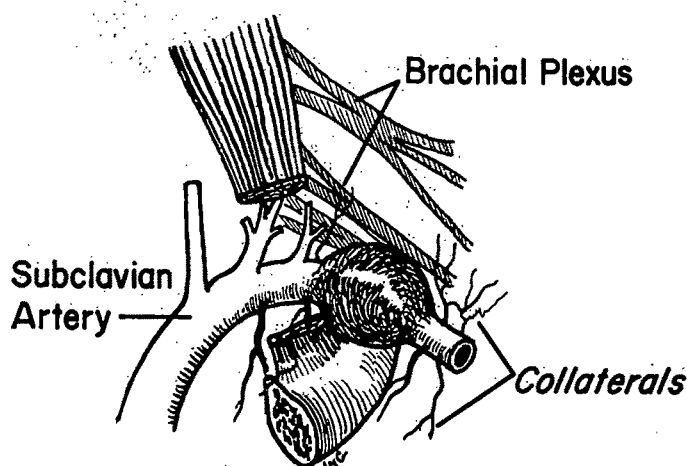


FIG. 8: Rich collaterals around subclavian axillary complex. Proximal control is sometimes ineffective in this location.

have performed panendoscopy supported by esophagogram and arteriography. If these are negative, the patient is spared surgery.

Subclavian, Axillary and Brachial Injuries

There were 110 injuries of upper extremity vessels including 12 subclavian injuries. Arterial injury due to blunt trauma had a decreasing relative incidence from subclavian to the brachial. Three of a total of 12 subclavian injuries were due to blunt trauma. Two of 23 axillary artery injuries and 3 of 75 brachial artery injuries were caused by blunt trauma. Apparently this discrepancy in incidence is due to the relatively fixed position of the subclavian artery over the thoracic inlet, making it susceptible to blunt trauma. Due to the mobility of the arm, the brachial artery was apparently spared. Gunshot wound was the most common method in injury of the three vessels. Of special interest was the incidence of three false aneurysms of the subclavian artery which were not diagnosed early elsewhere, due to the misleading and deceptive presence of a radial pulse. When diagnosed late, brachial plexus palsy was present due to compression. As this type of paralysis renders the arm refractory to rehabilitation, arteriography in all instances of penetrating injury to the shoulder girdle and thoracic inlet should be routinely carried out.

The surgical approach to the subclavian axillary complex varied according to the level of injury. Left anterolateral thoractomy, midsternotomy, supraclavicular incision, and an infraclavicular incision with or without clavicular resection were carried out as needed. Occasionally a combination of these incisions as a trap-door type of thoracotomy was used. Even though proximal control was routinely obtained, frequently it was of only marginal benefit. Rich collateralization around the subclavian axis can result in profuse bleeding despite proximal control (Fig. 8).

Significant Indications for Arteriography. First Rib Fracture: Brachial Plexus Injury. A 10-year-old girl jumped out of an automobile moving at high speed. When brought to the emergency room she had multiple lacerations and abrasions. She was conscious, in no great pain, and the only functional abnormality detected at this time was confined to the region of the right shoulder and upper extremity. She could not move her right arm and did not have sensation present in the upper extremity. Examination revealed complete brachial plexus palsy. She also had absent radial and brachial pulses in the affected extremity, but a weak subclavian pulse could be felt in the supraclavicular area. Roentgenographic examination of cervical spine, thoracic outlet, and right shoulder region revealed no bony abnormality. She was taken to surgery and underwent a successful resection of a centimeter length of thrombosed axillary artery. Reanastomosis was by end-to-end suture (Fig. 8). At the time of surgery the brachial plexus was carefully examined and was found to have been completely avulsed with dorsal ganglia and roots from the vertebral column. Neurological repair was obviously impossible. Postoperatively she had excellent upper limb pulses but continued to have distressing loss of function due to the neurological deficit.

Comment. Since the brachial plexus and its primary branches are closely wrapped around the subclavian axillary artery complex, trauma resulting in brachial plexus injury should also be suspected of involving the adjacent artery. Careful examination of distal pulses is indicated, and if found normal, an arteriogram must be done to prove the absence of vascular injury. In the presence of obvious vascular injury, preoperative arteriogram will be very helpful. Thus, in either case, an arteriogram is indicated in this type of injury involving the brachial plexus.

A similar indication for arteriography exists in cases of trauma resulting in fracture of the first rib.²⁴ The first rib is rigidly articulated, and further closely protected by the overlying muscles and bones of the shoulder girdle. The first rib apparently is among the most well-anchored structures in the bony thorax and is seldom fractured by trauma. Detectable fracture of the first rib usually indicates that the causative blunt trauma was of great violence and severity. Since the subclavian and axillary arteries are closely related to the first rib, it is not surprising that a high incidence of vascular injury in this area occurs with first rib fractures.

Abdominal Visceral Arteries

There were 26 visceral arterial injuries of which 4 were hepatic, 8 renal, 5 splenic, and 9 other types. Two of the 4 patients with hepatic artery injuries died in shock. Of the eight renal artery injuries, two were due to blunt trauma, one being a tornado victim. There were 4 nephrectomies and two deaths in the group. All but one of the 4 patients who underwent primary repair of the renal artery sur-

vived. Renal vascular hypertension was not documented in any of the survivors.

Femoral Arteries

There were 22 common femoral arterial injuries, 51 superficial femoral, and 11 injuries of the profunda femoral artery. Four injuries of the profunda femoral occurred at its origin, usually with some destruction of the common and superficial femoral arteries. In one patient, the compound saphenous vein graft, as shown in Figure 9, was used to reconstruct all the three vessels involved.

Popliteal Artery Injuries

Nineteen popliteal artery injuries were amenable to reconstructive arterial surgery. In addition, one case of shotgun wound to the popliteal fossa resulted in primary amputation as the extremity was mutilated beyond repair. The major mechanism of injury was gunshot wound, 3 of which were due to shotguns. There were 2 stab wounds to the popliteal artery and an additional 7 cases resulted from blunt trauma. Associated injuries included 4 posterior dislocations of the knee, 3 fractures of the femur, and one fracture of the tibia. All the shotgun wounds were associated with femoral fractures. All cases of popliteal artery injury presented with a cold, ischemic foot with uniform loss of pedal pulses except for one case which proved to be a false aneurysm of the popliteal artery with patent distal runoff. In all other instances at operation the artery was found to be either lacerated or transected. The type of arterial repair consisted predominantly of end-to-end anastomosis (11 cases), but three saphenous vein grafts and 2 Teflon grafts were used in 5 other cases. In one instance, lateral suture provided adequate repair. There were two cases (both of which resulted in amputation) in which proximal ligation and sympathectomy were used as procedures of choice. In the first instance, which was due to blunt trauma, the proximal artery was isolated but a considerable portion of the popliteal artery was completely destroyed and the distal end had retracted deep into the posterior compartment. Reconstruction was not considered feasible, as the injury was 4 days old, and proximal ligation of the artery resulted. In the other instance the cool extremity was the presenting feature, associated with posterior dislocation of the knee but an arteriogram revealed an intact popliteal artery with distal circulation. Instead of exploring the artery, a sympathectomy was done in the mistaken belief that an absence of radiological lesion insured anatomical integrity. Following eventual amputation, pathological examination revealed a lacerated popliteal artery which had subsequently thrombosed. The amputation rate was exceedingly high in this group, amounting to 30% including the single instance of primary amputation already cited. Of the other patients, all but two had

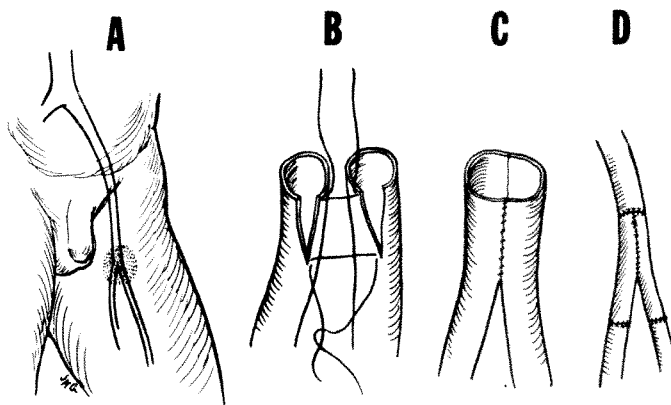


FIG. 9. Compound saphenous vein graft for reconstruction of deep and superficial femoral arteries.

good distal pedal pulses following surgery; one had a warm, non-ischemic foot, and the other had a cool foot with marginal circulation. During followup the latter patient had not had ischemic symptoms. There was one instance of causalgia which was successfully treated by sympathectomy.

Several features in this group of patients were analyzed in view of the high amputation rate. Three of the 5 patients who underwent amputation clearly had the longest ischemia time (from injury to restoration of circulation) of the whole group: 3 days, 4 days, and 4 days respectively. In the majority of others, the average ischemia time was 6 to 12 hours, but there were two instances in which the ischemia time was 24 hours and 40 hours respectively. Both of the latter cases had satisfactory end results. There were other similarities between the 5 amputated cases with regard to certain clinical features. All 5 cases were either due to severe blunt trauma, or shotgun wounds which resulted in extensive disruption of the popliteal fossa along with accompanying veins and the bones of the region. In all of these cases primary arterial repair was inadequate, or ultimately became compromised due to other reasons. In one instance the popliteal artery was ligated without repair; in another, lateral injury of the popliteal was missed and no repair was done; in two others the saphenous vein graft ultimately stopped functioning due to extensive muscle necrosis; and in one instance there was secondary bleeding leading to ligation of the saphenous vein graft. There were 4 posterior dislocations of the knee in the entire group of 19 popliteal injuries, and in 2 of the 4 patients amputation ensued. The delay in diagnosis of the arterial lesion accompanying this treacherous injury has been documented by others.¹⁸

Arteriovenous Fistulae

The distribution of 38 arteriovenous fistulae that were seen primarily after trauma are represented in Figure 10. In addition, 3 arteriovenous fistulae occurred as a com-

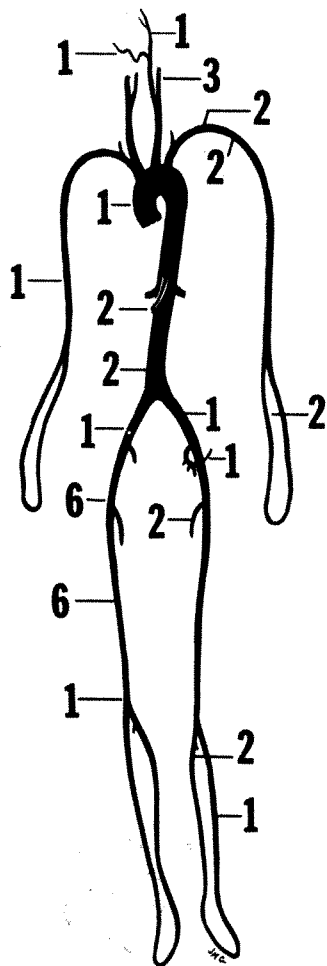


FIG. 10. Anatomic distribution of 38 arteriovenous fistulae.

plication of arterial surgery for trauma. In all but 4 instances the causative agent had resulted in a penetrating wound. Gunshot wounds were responsible for the majority of cases. There were two carotid-cavernous sinus fistulae due to blunt trauma. Considering the overall preponderance of arterial injuries occurring in the extremities, it is not surprising that more than 50% of all arteriovenous fistulae occurred in this location. The most common form of presentation was a detectable bruit or a palpable thrill. A palpable mass was detected over the fistula in some instances. In 5 instances congestive heart failure was present, almost always due to fistulization of a major artery and vein either in the trunk or head and neck. The single exception was a large fistula between the common femoral artery and vein. There was only one infected fistula in this series.

There was considerable delay in diagnosis. The interval between occurrence of the injury and repair varied from a few hours to several years. There were seven cases in which 4, 5, 12, 16, 20, 30, and 34 years respectively passed from the time of injury before repair was effected. Thirty-six of the 38 patients underwent surgery; two patients refused operative correction. At the time of surgery in 5 cases, a false aneurysm was found in associa-

tion with the fistula. All 5 were excised. True proximal arterial dilatation (Fig. 11) or aneurysm associated with long standing cases¹⁰ was encountered in 3 patients in this series. The predominant method of repair was division or excision of the fistula combined with reconstruction of the artery and the vein as well (25 cases). Saphenous vein grafts were necessary in 4 cases and in one instance during the early experience a juvenile aortic homograft was used. In 11 cases, due to the functional insignificance of the artery involved, or due to inaccessibility of the artery for reconstructive repair (*e.g.*, internal carotid), ligation of the feeding artery and if possible the vein as well was the major surgical procedure. Using these techniques, all but two patients had satisfactory closure of the fistula with excellent results. In these two exceptions, residual bruits were discovered postoperatively but there was little functional impairment. Among those patients who ultimately got an excellent result, two patients were re-explored due to hemorrhage, one patient had a wound infection, another patient required sympathectomy for causalgia. The use of a sterile stethoscope at operation can increase the certainty that all fistulae have been closed, an especially important consideration in shotgun injuries.



FIG. 11. Aneurysmal dilatation of left iliac vessels in a patient with left deep femoral arteriovenous fistula. There was a 34-year delay between injury and repair.

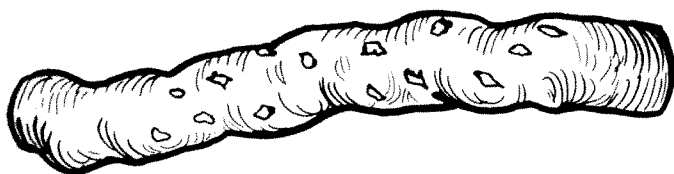


FIG. 12. "Pock mark" lesion of artery due to shotgun injury.

Discussion—Special Problems

Blunt Trauma to Extremity

The vast majority of blunt trauma to vessels of the extremity are associated with bone fractures. While the diagnosis of arterial injury in this instance seldom poses difficulties to the alert clinician, the orthopedic problem can provide diagnostic diversion to the unwary and the arterial injury may go unnoticed. Sometimes surprisingly mild blunt trauma can cause vascular injury and thrombosis without evidence of bone, soft tissue, or skin injury. An arteriogram is essential in these instances to localize the precise site and extent of the thrombosis. At operation, the external appearance of the artery can sometimes be deceptive when no external evidence of contusion or discoloration is seen. If thrombosis is localized and rich collaterals are present, distal pulsations may be misleadingly present. It has been shown that the intima of the artery is more susceptible to the effects of trauma than are the other coats.¹³ Consequently, intimal injury and thrombosis may be more extensive and may not extend to the adventitia. A surgical procedure varying from thrombectomy to resection of the artery may be required depending upon the extent of the injury.

Shotgun Injuries

The 37 shotgun injuries reviewed in this series presented a wide range of problems which were extensive and often serious. Almost invariable association of extensive skin, soft tissue, nerve and comminuted bone injury was impressive. The vascular injury itself was often due to multiple pellets with destruction of a long stretch of artery (Fig. 12), often requiring a vein graft for repair. Wound debridement and the orthopedic part of the procedure assumed equal importance with the arterial repair. The dead muscle had to be excised back to bleeding tissue, but judgment was required to retain enough viable tissue to provide a bed and cover for the vascular reconstruction. The infection rate was high with a significant incidence of secondary bleeding from the artery, usually requiring high ligation. The amputation rate following shotgun injury was three times the rate for other types of injury. Frequently, even when a successful vascular repair and wound healing had been achieved, the repaired extremity was difficult to rehabilitate due to concomitant nerve injury.

When a combination of these numerous adverse fac-

tors co-exist in a shotgun injury, it may be judicious occasionally to carry out primary amputation.

Fractures with Arterial Complications

Apart from arterial and bone injury from the same blunt trauma, it is well known that fractures occasionally are primary causative agents for arterial injury (Fig. 13). The actual method of vascular injury may be due to a wide variety of pathological mechanisms.²¹ Not infrequently the diagnosis of arterial injury is delayed or entirely missed. In the upper limb the association of Volkmann's contracture with supracondylar fractures is well known. When acute arterial injury occurs in association with bone fractures, irrespective of the causative mechanism, priorities as well as the type of management are unsettled. Stabilization of fractures before arterial repair is widely advocated in the literature.^{19,21} The rationale for this sequence is to forestall injury to the vascular repair by an unstabilized fracture. We ourselves have been more concerned with speedy restoration of distal perfusion and have usually given primacy to the arterial repair before the orthopedic procedure. Soft tissue debridement which is speedily accomplished is undertaken at the same time as the arterial repair, and

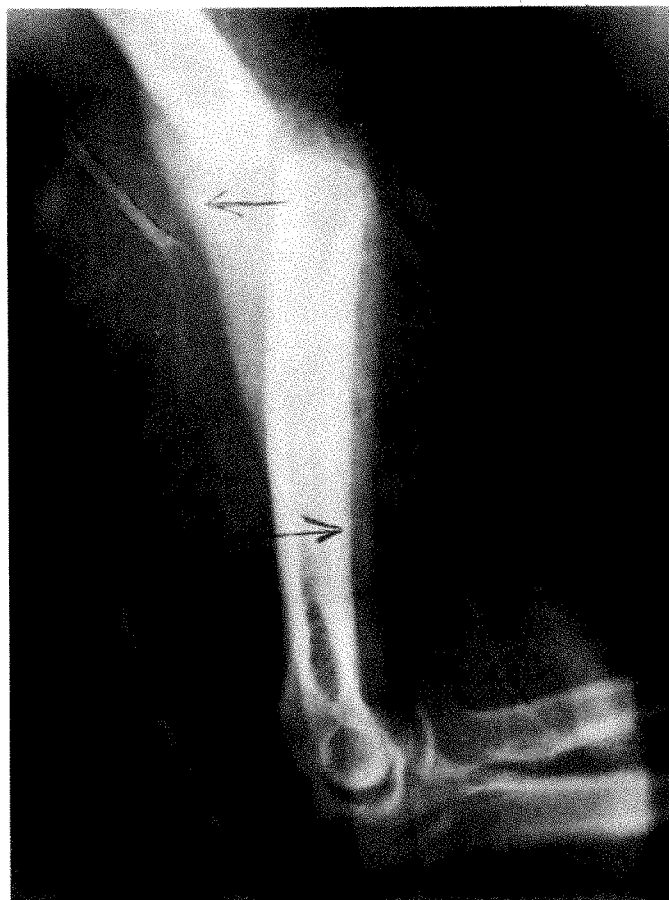


FIG. 13. Brachial artery injury due to fracture of the humerus.

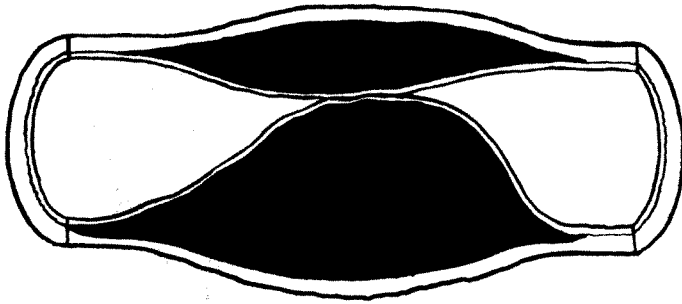


FIG. 14. Iatrogenic injury; limited arterial dissection from arterial puncture.

general anesthesia with full muscle relaxation is necessary. Preliminary fracture reduction is rapidly accomplished if bone fragments are in the way. After satisfactory restoration of blood flow, final reduction and other orthopedic procedures which may be necessary are carried out. In our experience, we have not had occasion to regret this inversion of the sequence generally advocated by others. Additionally this had the important merit of reducing time of distal ischemia, which may be crucial in such locations as a popliteal artery.^{6,18} Some authors have improvised a compromise, using a preliminary thrombectomy, heparinization before the fracture is stabilized, and the arterial repair then carried out last.²¹ One group has advocated temporary arterial shunts while the orthopedic procedure is accomplished.⁶ We have used the temporary shunt once, but prefer primary arterial repair. The vast majority of fractures encountered in this series were stabilized by external fixation for fear of infection associated with compound and comminuted fractures. Internal fixation may be used in arterial injuries associated with simple fractures. The experience in Viet Nam¹⁹ tends to support this general approach.

Iatrogenic Injuries

The problem and variety of iatrogenic arterial injuries have shown an alarming increase in recent years. This is undoubtedly due to the recent increase in diagnostic radiographic, therapeutic, and monitoring procedures requiring arterial puncture. Brachial artery injuries due to cardiac catheterization are frequently seen. Perhaps a larger number of patients with an absent or weak pulse but with a viable warm extremity after catheterization do not come to the surgeon's attention. We have infrequently seen children with femoral arterial occlusion following cardiac catheterization. Another type of injury which is being increasingly seen in the intensive care unit is a cyanotic hand from a radial artery cannula for pressure monitoring. Generally, there are no perfusion problems of the hand if the cardiac output is in the adequate range. In the several cases we have seen, viability of the hand has been maintained with improvement in the patient's general status, and we have not often had to

treat gangrene from this complication. One instance of carotid injury from subintimal infection of contrast material for arteriography is included in this series. Other bizarre instances of iatrogenic arterial injury that we have witnessed include carotid thrombosis from an attempted internal jugular venipuncture, subclavian-internal mammary arteriovenous fistula during placement of a central venous pressure line, and femoral arterial occlusion due to sharp instrumentation that was being used in total hip replacement. The arterial pathology in the last instance was a limited dissection with thrombosis. (Fig. 14).

Thrombosis and Spasm

Early vascular literature is replete with instances of vascular spasm relieved with return of pulse. The advent of arteriography has revealed these instances of "spasm" to be due usually to arterial thrombosis and intimal disruption.²¹ Return of the pulse was probably due to collaterals. At operation a spastic artery is almost invariably associated with thrombosis, and an arteriotomy should be done. In this series there were only two instances of true arterial spasm without thrombosis. In the same context, sympathectomy and sympathetic blocks have been of little value in the management of acute arterial injuries in our experience.

Retroperitoneal Hematoma: To Explore or Not Explore?

Judgment is required in deciding whether or not to explore retroperitoneal hematoma.^{1,5,23,27} There is little choice but to explore a retroperitoneal hematoma which is expanding, pulsatile, and a source of blood volume loss. On the contrary, some advocate nonexploration when these criteria are not present.¹⁴ It has been argued that a majority of nonpulsatile retroperitoneal hematomas are due to self-limiting venous injuries and meddlesome exploration can be the cause of further hemorrhage. In our experience significant retroperitoneal arterial injury may be present even when the hematoma is small, nonexpanding and nonpulsatile. Sometimes pulsations may be difficult to perceive, and expansion may not yet have occurred. Based on these considerations, we now favor exploration of most retroperitoneal hematomas provided other relative contraindications are absent. For example, we would be reluctant to explore a benign appearing retroperitoneal hematoma when there is massive peritoneal contamination or when a bleeding diathesis secondary to massive transfusion exists. Immediate repair of significant arterial injury is generally easier than would be the case at a later time. Arteriography can be very helpful in such patients.

Early Graft Thrombosis: Prompt Exploration

Intraoperative graft thrombosis is almost always due to technical problems with the vascular anastomosis. Revision of the anastomosis is called for with the aid of

arteriograms if necessary. Resorting to artificial methods of maintaining patency, such as heparinization in the face of technical problems, usually does not succeed for more than a few hours. Causes of late thrombosis of the graft, such as poor inflow and run-off seen in arteriosclerotic disease, are usually absent in the surgery of arterial trauma. Unrecognized retention of thrombus in the distal arterial tree, and involvement of the graft from infection, are the most frequent causes of late graft thrombosis in this type of surgery. The overall incidence of graft failure has been very low in our experience with traumatic arterial surgery (3%).

Fasciotomy: Timing and Techniques

Fasciotomy is an invaluable adjuvant to arterial surgery in the extremities, especially when considerable swelling of the operated limb is expected.¹⁵ Such instances would include extensive soft tissue injury after a shotgun blast, injuries compromising venous drainage of the limb, or injuries associated with prolonged shock or a long ischemia time. To be effective, fasciotomy has to be performed early. It is also useful in advancing the level of amputation distally where, despite aggressive arterial reconstructive surgery, limb circulation remains marginal. It should be emphasized in this context that fasciotomy should never be used as a temporizing measure when a vascular procedure is indicated. We generally prefer subcutaneous fasciotomies done through small skin incisions over both the anterior and posterior compartments of the leg. Occasionally the peroneal compartment as well as the deep posterior compartment are added. When skin constriction is a factor in vascular compromise, we have not hesitated to do extensive transcutaneous fasciotomies. We have occasionally used the fibulectomy method¹⁵ of decompressing the leg compartments, when extensive comminuted bone injury is present.

Graft Materials

Since infection is the most common nonfatal complication, grafts of any type should be avoided. Fabric grafts were used infrequently when the saphenous vein was inadequate in size or otherwise unavailable. Cephalic or other veins were used only occasionally, since they are technically difficult to handle and are prone to aneurysmal dilatation. Compound saphenous vein grafts (Fig. 9) can be constructed to replace medium-sized arteries.

Anticoagulation? Dextran?

We routinely administer heparin parenterally during the operation for arterial trauma. This has been more reliable than local heparinization. Intraoperative hemorrhage has seldom been a problem, and protamine may be administered for reversal. At times the heparin has been allowed to disappear gradually with metabolic degradation. In contrast, postoperative heparinization causes

bleeding and is not used. When support to maintain arterial patency is required, we have generally used low molecular weight dextran for 48-72 hours. Increased oozing from raw areas can be a problem but has been controlled by wound drainage for a brief period postoperatively where indicated.

Fogarty Catheterization

We commonly employ Fogarty catheterization in the distal artery in cases of arterial trauma, even when backbleeding is excellent. It is general knowledge that such backbleeding does not rule out the presence of distal thrombus, and this has been our experience. Occasionally, we have used catheter thrombectomy of the associated vein. There is some evidence that the amputation level is beneficially advanced distally by temporary maintenance of venous patency.¹⁸

Special Technical Considerations

Not infrequently after arterial repair distal pulses are not immediately felt but become obvious after a period of hours, even days. Under these circumstances it is important to confirm arterial patency by an intraoperative arteriogram. In the postoperative period persistence of patency can be conveniently ascertained by using the ultrasonic flow probe. We have found serial measurements of ankle pressures with the ultrasonic flow probe very useful in indicating the state of perfusion.

Drains are generally avoided after arterial surgery, but they are sometimes unavoidable and we have not hesitated to use them when indicated. Usually a closed system of drainage is preferred, and they are removed usually by 48 hours.

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DISCUSSION

DR. FRANK SPENCER (New York, New York): I appreciated the opportunity of reading this impressive manuscript beforehand, for with the 350 cases reported, it is not possible to analyze the data in the short time available for presentation. The manuscript clearly represents a significant contribution to the field of arterial injury.

I will make a few specific comments. First, arterial spasm was rare, recognized only twice among 350 cases. I think most patients would benefit if this term virtually disappeared, for the word "spasm" often connotes a harmless condition that will improve without operative therapy. In most patients the more serious injury of contusion, disruption of the intima, and thrombosis is present which clearly requires operation for correction.

A second point is the increasing usefulness of angiography. In someone with multiple penetrating injuries, as from shotgun pellets, uncertainty can readily exist about whether an arterial injury is present. An angiogram is the simplest method to exclude an arterial injury, as opposed to either watchful waiting or widespread surgical exploration of the artery in question.

Uncertainty remains about the best therapy for injuries of the carotid artery. One question is whether a shunt should be used at the time of operation. This was not used by Dr. Hardy with good clinical results. Another question concerns therapy if a neurologic injury is present. The one patient reported to have been hemiplegic for two days, with recovery after arterial repair, is impressive. Others have reported fatal hemorrhagic infarcts following arterial repair in such instances. This remains one of the frontiers for further study.

Iatrogenic arterial injuries are becoming increasingly frequent. A few cases are described in the manuscript resulting from cannulation of the radial artery. Although this is a popular technique, we have at least two patients in New York in which amputation resulted from the procedure, one patient requiring amputation of all four fingers. Another one was barely retrieved by reoperating and reanastomosing the radial artery.

Injuries of the popliteal artery remain an unsolved problem. The amputation rate for popliteal arteries in this series is 30%, similar to that in most reports. I personally think, supported by Dr. Hardy's movie, that when there is extensive loss of soft tissue, with fracture of the bone and loss of the popliteal vein, that attempts at primary repair should be abandoned. Instead I believe one of the extra-anatomic bypasses should be performed as an initial procedure to maintain viability for a few weeks while healing of the primary wound can be obtained. Subsequently elective reconstruction of the popliteal artery can be done in much more favorable circumstances. I should emphasize that this is a theoretical concept, for I do not believe significant data are yet available for this approach.

I would question the authors about the use of heparin. I personally

would not recommend its use for most artery injuries because of the associated bleeding. Infection was a common complication in this series, though usually responding to treatment. I wonder if bleeding, hematoma formation, and wound drainage may have contributed to the frequency of infection. A second question is the frequency of secondary wound closure. In most arterial injuries, there is usually a significant degree of contamination; so after arterial repair, as demonstrated repeatedly in different military conflicts, secondary wound closure can be effectively employed with a very low incidence of infection.

Finally, I wonder if it was ever possible to retrieve a patient with an infected arterial repair short of an extra-anatomic bypass? This is the critical problem in vascular surgery. Arterial repair can almost always be done, for usually the arteries injured are normal arteries in young people. Infection, however, remains a dreaded problem, for it usually results in either loss of limb or life.

DR. G. RAINEY WILLIAMS (Oklahoma City, Oklahoma): We are all indebted to Dr. Hardy and his productive department and I think this will be another significant contribution to our knowledge. I'd like to make two points. The first has to do with concern about the policy of liberal exploration in the expectation that vascular injury may be present. Dr. Hardy did not mention this, but we have followed Dr. Shires' advice in this regard and have been interested in knowing whether or not this is justified. (Slide) This summarizes our experience with positive and negative exploration for vascular injury in the past several years. You will note that, despite a marked increase in the number of explorations, the percentage of positive explorations has remained about the same. Analysis of the negative explorations has led us to the position that the very low mortality and a 31% incidence of significant associated injuries justifies continuing the policy of routine exploration.

Second, I would like to present an unusual patient. A young woman was admitted to our hospital several days after an automobile accident. She sustained multiple injuries and, on the third or fourth hospital day, underwent open fixation of an ankle fracture. The operator noted that the wound did not bleed vigorously when the tourniquet was removed and a day or two later the toes were noted to be frankly gangrenous. The patient was referred to our institution and promptly underwent aortography. (Slide) This film shows a fairly abrupt cut-off in the midabdominal aorta and this subtraction study reveals delayed filling of the distal aorta and iliac vessels. This closed transection of the intima of the abdominal aorta with obstruction was easily repaired. Its earlier detection might have resulted in salvage of the foot.

Again, we appreciate this report by Dr. Hardy and his associates.

DR. DANIEL B. NUNN (Jacksonville, Florida): I want to call to your attention an unusual aortic injury, namely, dissection of the abdominal aorta following nonpenetrating abdominal trauma.

All of the reported cases of this injury, which, as far as I can determine, number fewer than ten, have been complicated by thrombosis of the abdominal aorta and/or its visceral branches. Paraplegia of variable duration has been present, and is probably caused by severe ischemia affecting the peripheral nerves of the lower extremities, rather than spinal cord ischemia or injury per se.

To date I have treated two patients who developed traumatic dissection of the infrarenal aorta after a steering wheel injury to the lower chest and upper abdomen. Interestingly enough, both of these patients were driving pickup trucks and not wearing a seat belt when the accidents occurred. Since the seat in the trucks was high with respect to the steering wheel level, the impact between the driver and the steering wheel resulted in blunt trauma directed primarily to the driver's upper abdomen.

In each patient the dissection was complicated by thrombotic occlusion of the infrarenal aorta and iliac arteries, and extensive arterial thromboses in the lower extremities. Neither patient had preexisting clinical arterial disease, but abdominal x-rays showed a moderate degree of aortic calcification.

Both patients underwent operation less than three hours after their accident. The infrarenal aorta and common iliac arteries were resected, and replaced with a Dacron graft. Also, a peripheral thrombectomy was performed, and Fogarty catheters were passed from the groin to the ankle level bilaterally.

Postoperatively, only femoral pulses were noted, and paraplegia persisted. The patients exhibited findings compatible with the myopathic nephrotic metabolic syndrome associated with massive acute arterial occlusions, and which has been described by Dr. Henry Haimovici. Specifically, there was rigidity of the extremities resembling rigor mortis, myoglobinuria, and severe acidosis.

There were no gangrenous skin changes in the lower extremities. Despite intensive treatment with sodium bicarbonate and intravenous heparin, both patients expired less than 48 hours after operation. The extensive thrombosis in these patients suggested the possibility of an increased clotting mechanism triggered by the injury. Indeed, in one patient who was studied in this regard there were laboratory findings compatible with DIC.

At any rate, it would seem that recovery from this type of injury, with the associated severe clotting of the lower extremities, would require early, bilateral high-thigh amputation, in the absence of gangrenous skin changes, unless some suitable method could be found to open small vessel channels.

With this in mind, I wish to ask Dr. Hardy if he has had any experience with pit viper venom, known as Arvin, or venacil, as a thrombolytic agent. In one of these patients I had attempted to obtain some of this material, but unfortunately my patient expired before it arrived.

DR. HILARY H. TIMMIS (Royal Oak, Michigan): I would like to bring to the attention of the Society a lesion which is perhaps the most common of all arterial injuries, which Dr. Hardy, in charity, has not mentioned. I refer to occlusion of the brachial artery following cardiac catheterization, particularly when the study is performed for coronary arteriography.

With the emotional impact of cardiac disease, and the outcome of cardiac catheterization, these patients will commonly neglect their symptoms of arm claudication until they have returned home, and with time their complaints will gradually improve especially in the milieu of restricted activity.

Because of the frequency of this problem which involves 5–10% of patients, we have asked our cardiologists to caution the patients regarding the possible loss of their radial pulse and the presence of some arm claudication following catheterization. The problem is amenable to simple exploration under local anesthesia and, invariably, thrombectomy to restore blood supply below. In the many arteries that we have explored, spasm has simply not been present. When exploration of the brachial artery is carried out promptly, hospitalization is not prolonged.

MAJOR GENERAL CARL W. HUGHES (Washington, D.C.): I have been fortunate enough to be involved in two sizable studies of vascular injuries. With the Korean War we studied 304 acute arterial injuries, part of which were Dr. Spencer's, and 215 traumatic arteriovenous

fistulas and aneurysms; and as Dr. Hardy remarked, because of the relations in the neurovascular bundle, some two-thirds of those were fistulas. The rest were false aneurysms.

Our most recent study was of some 7500 acute vascular injuries from Vietnam. Of course, most of these are high-velocity injuries, and that study is still in progress, and will continue for a long period of time.

I want to say how much I enjoyed Dr. Hardy's paper, and would like to add one thing that our studies are bearing out, and that is the importance of repairing major veins. Venous repair appears particularly important in the success of popliteal artery repairs.

DR. SESHADRI RAJU (Closing discussion):

Dr. Spencer rightly emphasized the rarity of arterial spasm as a cause of distal ischemia in arterial injury. Referrals are sometimes obtained several days after the arterial injury, which had been watched as a possible case of "spasm." The "spasm" invariably turns out to be something more organic and serious. In our entire series of 360 injuries there were only two authenticated, true arterial spasms. We fully concur with the emphasis on the rarity of this condition. Too many limbs are lost because of procrastination consequent to an incorrect diagnosis of "arterial spasm."

We do not have a rigid policy about mandatory exploration of neck wounds as advocated by Dr. Shires. We explore the patient immediately if arterial injury is obvious. Otherwise, in a stable patient, we prefer arteriography to prove or disprove the presence of arterial injury.

In our series, 52% of all patients had arteriography, which shows our heavy reliance on this technique as a preoperative measure.

In AV fistula we have found the intraoperative use of sterile stethoscope of great value in deciding whether one has closed the fistula or not. This is especially important following shotgun injuries, where multiple pellet perforations may have produced more than one AV fistula.

We have had experience with four or five patients whose hands were precarious following radial arterial cannulation for monitoring blood pressure; but thus far all such patients have died due to their primary pathology elsewhere, so we did not have occasion to do anything about the hand injury. It appears that a patient who is in very poor general condition and has a poor cardiac output, is primarily the type of patient who would present with pregangrenous changes in the hand following radial artery cannulation. Relatively healthy patients who are going to recover probably exhibit enough collateral perfusion that there are usually no lasting effects from radial arterial cannulation. However, some surviving patients will surely exhibit finger necrosis.

We fully concur with Dr. Spencer's remarks on the difficult problems of popliteal artery and carotid artery injuries. We do not believe in postoperative heparinization for vascular trauma. However, we do use intraoperative heparinization, 100 mg in an adult patient, given intravenously as a single dose, and we usually reverse this. Occasionally we let it disappear by metabolic degradation. Again, we do not use heparin in the postoperative period because hemorrhage may occur.

We have had approximately 50 wound infections in this whole series, 35 of which were superficial infections. Fifteen were deep infections involving the arterial repair, and half of them ended in amputation. The particular patient that Dr. Hardy presented, showing the subscrotal vein bypass, did have infection of this type, involving his left common femoral artery, which ultimately required ligation. This precipitated the need for the vein bypass. We have had a number of secondary closures for these wound infections, but I am unable to give you precise figures on this.

Dr. Nunn, we have not had any experience with viper venom, and I thank you for adding those two interesting cases to this discussion.

Dr. Timmis, thank you for your comments on cardiac catheterization, and the problems with iatrogenic brachial artery injuries. We have had approximately 20 similar cases, virtually all of which were treated successfully.

We are indebted to General Hughes for his leadership in this whole area of arterial trauma; he has rightly emphasized the importance of venous repairs. Following this lead, we ourselves are paying increasing attention to venous restoration in the management of arterial injuries. I would like to thank the Association, especially Dr. Sabiston and Dr. Warren, for the privilege of the floor.

Surgical Management of Abdominal Aortic Aneurysms:

Factors Influencing Mortality and Morbidity—A 20-Year Experience

JESSE E. THOMPSON, M.D., LARRY H. HOLLIER, M.D.,
R. DON PATMAN, M.D., ALFRED V. PERSSON, M.D.

Abdominal aortic aneurysmectomy is being performed with progressively lower operative mortality and morbidity. Three hundred thirty seven private patients have had elective aneurysm repair since 1954. Factors affecting mortality and morbidity in the last 108 cases are analyzed. Seventy-four per cent of patients had pre-existing disease, either cardiac, pulmonary, renal, cerebrovascular, diabetes mellitus, or hypertension. Six patients died following operation, a mortality rate of 5.5%. One died of pulmonary and 5 of cardiac causes. No patient died of renal failure or required dialysis. A significant feature of management is the regimen of fluid therapy using dextrose in lactated Ringer's solution during and after operation to minimize hypotensive and renal complications. No patient developed a wound infection, graft infection, wound dehiscence, stroke, or intestinal ischemia. Serious postoperative complications were largely cardiac or pulmonary. Despite recent liberalization of indications for operation, comparative figures show continued reduction in operative mortality from 17% during 1954-1961, to 7.4% during 1962-1967, to 5.5% in the 1968-1974 era. This declining mortality is related to earlier diagnosis using non-invasive methods (sonogram), simplified operative techniques, improvement in fluid management, innovations in cardiopulmonary therapy, and recognition and proper handling of unusual manifestations of aortic aneurysms.

SINCE THE REPORT of Dubost, Allary, and Oeconomos⁷ in 1952 of the first resection and homograft replacement of an atherosclerotic abdominal aortic aneurysm, great strides have been made in the treatment of this disease. The natural history of aortic aneurysms has been more clearly delineated, indications for operation have been more precisely defined, surgical management has

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become standardized, unusual manifestations and complications have been observed, and operation is being performed with progressively lower mortality and morbidity rates.

This report is a continuation of previous clinical investigations of aortic surgery, based on a 20-year experience with more than 900 operations for both aneurysmal and occlusive disease, beginning October 20, 1954. Of these, 337 operations were performed electively for unruptured abdominal aortic aneurysms, 72 were emergency procedures for ruptured aneurysms while the remaining procedures were for aortoiliac occlusive disease. In a previous paper²⁰ we reviewed the operative mortality for the first 229 elective operations for aneurysm. The present report reviews the last 108 cases subjected to elective repair and analyzes factors influencing the improvement in mortality and morbidity rates.

From 1968 through mid-1974, 108 private patients were subjected to elective operation for abdominal aneurysm. There were 93 men and 15 women, whose ages ranged from 46 to 85 years with an average age of 66. Twenty-five per cent of the patients had concomitant aortoiliac occlusive disease.

The occurrence of numerous other diseases, especially complications of atherosclerosis, in patients with aortic aneurysms is a well documented fact.^{6,17} Table 1 lists the pre-existing diseases among our 108 patients. Thus 74% had one or more additional serious conditions. Eight patients had had carotid endarterectomy prior to

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TABLE 1. *Pre-Existing Diseases Among Patients with Abdominal Aortic Aneurysms*

	Number of Patients
Total with pre-existing diseases	80
I. Cardiac disease	43
1. Previous myocardial infarction	29
2. Congestive failure	17
3. Angina pectoris	15
4. Abnormal ECG	8
5. Valvular disease	2
6. Previous pericarditis	1
II. Hypertension	43
III. Diabetes mellitus	8
IV. Chronic obstructive pulmonary disease	19
V. Renal disease	19
1. Elevated BUN	11
2. Pyelonephritis	3
3. Stones	3
4. Previous nephrectomy	3
5. Non-functioning kidney	2
6. Polycystic kidneys	1
7. Horseshoe kidney	1
VI. Previous carotid endarterectomy	8
(Ten operations)	

aneurysm repair. It is thus obvious that one is dealing with a group of elderly patients with multiple high-risk factors.

General Principles of Management

Diagnosis of abdominal aneurysm is usually easily made by the presence of a palpable pulsating mass or a line of calcium on an x-ray film, especially in the lateral projection. While some surgeons advocate routine performance of contrast aortography for all known or sus-

pected aneurysms, we have reserved aortography for those cases in which the diagnosis is questionable, there is associated occlusive disease, or there may be problems with the renal arteries.

Recent employment of non-invasive techniques for confirmation of the diagnosis of aneurysm in questionable cases and for screening of patients with known atherosclerosis in other areas promises to be a major advance and should lead to earlier and more accurate diagnosis in many instances. B-mode ultrasonic scanning and radionuclide aortography are the methods currently under investigation.^{4,12,15} Our experience has been with the ultrasonic scan, or abdominal sonogram (Fig. 1), and to date has been extremely rewarding. Measurements of aneurysmal size on the scan have correlated closely with those made in the operating room. With this technique it is also possible to follow any increase in size of aneurysms which for one reason or another were not operated upon when first seen.

In addition to the usual complete preoperative evaluation, patients with any degree of chronic obstructive pulmonary disease undergo pulmonary function studies and are then given IPPB therapy preparatory to aneurysmectomy. This has been one of the most important improvements in the pre- and postoperative management of these patients.

The technique of abdominal aneurysmectomy has become fairly well standardized. Minimal dissection is the essential feature. No effort is made to remove the aneurysm *intoto* as was done in the early days. The sac is simply opened, all clots are evacuated, and the lumbar arteries are sutured from within. This single step reduces operative complications tremendously. A pre-clotted knitted dacron graft is then sutured into place with da-

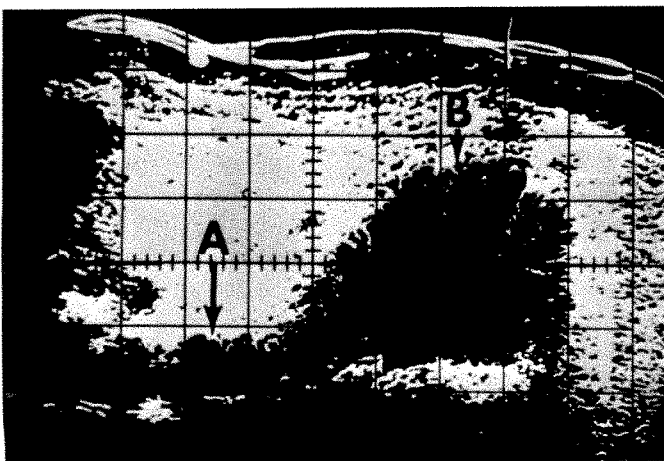
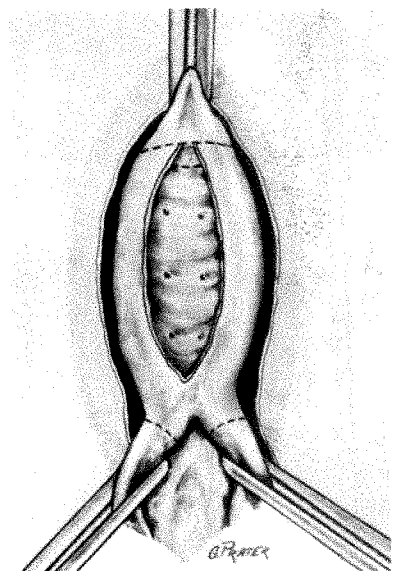


FIG. 1. Ultrasonic B-mode scan of large abdominal aneurysm. (Sonogram) At A the aorta is of normal diameter, measuring 2.7 cm. At B the infrarenal aortic aneurysm measures 9 cm in antero-posterior diameter. Each large square on the film denotes 3 cm while each small division on the scale denotes 6 mm. Longitudinal section with head of patient on the left.

FIG. 2. First step in aortic aneurysm repair showing minimal dissection of aorta and iliac arteries and intrasacculary incision and exposure. No attempt is made to resect the aneurysm wall.



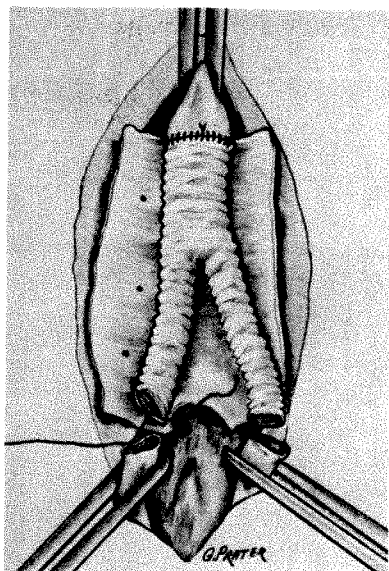


FIG. 3. A knitted dacron graft is sutured to the proximal aortic stump with polyester sutures. Bleeding lumbar arteries are sutured from within the aneurysm sac. Right iliac anastomosis begun.

cron sutures and the aneurysm wall, is sufficiently voluminous, covers the graft. Either a bifurcation or tubular graft may be used depending upon the aneurysm. Heparin is injected locally and systemically during clamping but is not employed postoperatively. Figures 2 through 4 illustrate the essential steps of a standard aneurysm repair.

One useful technical maneuver is shown in Figure 5. A

cuff of dacron is slipped over the upper aortic anastomosis prior to clamp removal. This cuff supports the suture line, reduces bleeding and isolates the anastomosis from small bowel.

Occasionally proximal control may be difficult, especially with inflammatory or ruptured aneurysms. One may obtain control at the level of the diaphragm manually, with a clamp, or with a special depressor. Another useful method is the insertion of a large Foley catheter through the aneurysm into the aorta above. Inflating the balloon controls bleeding temporarily and provides time for definitive control below (Fig. 6).

Proper fluid therapy during and after aortic surgery is of critical importance in preventing hypotensive and renal complications. We previously reported²⁰ in detail a regimen of fluid therapy for aortic surgery, which we have continued to use with certain refinements. Its basis is 5% dextrose in lactated Ringer's solution and is outlined in Table 2.

A liter of Ringer's is infused quickly at the beginning of anesthesia in order to promote urine flow. As a rule this solution is infused thereafter at the rate of about 500 ml/hr of operation. Blood is replaced volume for volume as lost. This allows for adequate blood pressure levels without vasopressors and for good urinary output of at least 50 ml/hr. Postoperatively one reduces the Ringer's sharply, giving only enough to replace extra-renal losses and extracellular fluid which is sequestered in the operative site and legs. During the first 24 postoperative hours

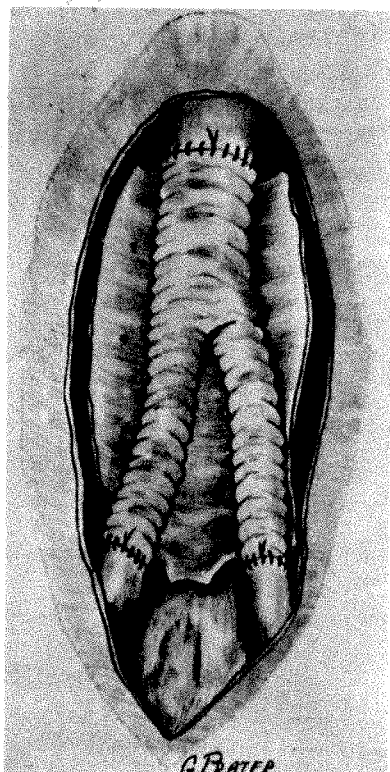


FIG. 4. Completed graft replacement for abdominal aneurysm. If the aneurysm wall is sufficiently voluminous, it is sutured over the graft, thus excluding the dacron from direct contact with bowel and other viscera.

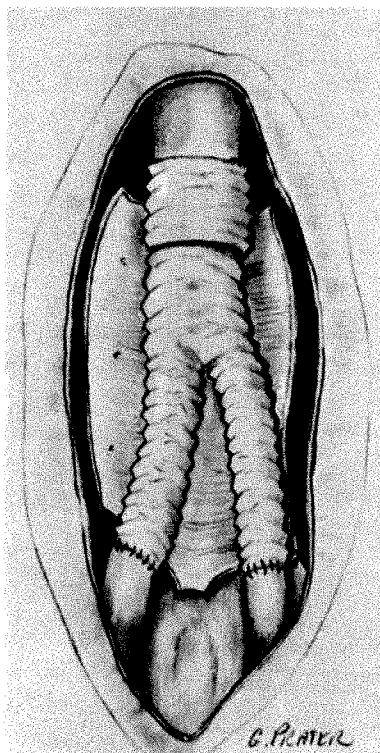
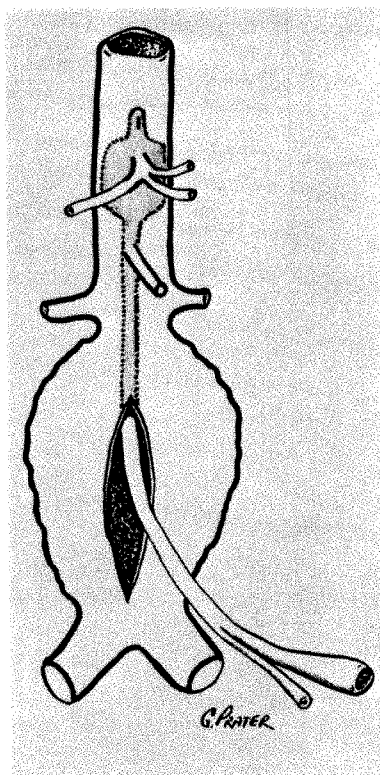


FIG. 5. A variant in the technic of upper aortic anastomosis, showing a cuff of dacron placed over the suture line. This cuff reduces bleeding upon clamp removal, obviates postoperative hemorrhage, supports the suture line and proximal cuff of aorta when the latter is thin or aneurysmal, and isolates the suture line from small intestine, largely eliminating the possibility of aortoenteric fistulas.

FIG. 6. Technic of proximal aortic control using a large Foley catheter in the aortic lumen. This method is useful for inflammatory aneurysms when the infra-renal aortic area cannot be dissected out, and for emergency control in ruptured aneurysms.



about 1 liter of Ringer's is used and the principal solution is dextrose in water, as in the second 24 hours.

One must use this regimen judiciously, as determined by the individual patient, in order to keep blood pressure and urinary output at appropriate levels but at the same time to avoid overload of the cardiovascular system. Hourly urine output is routinely recorded and intra-arterial and central venous pressures are monitored as indicated. It should be emphasized that the principal solution is 5% dextrose in lactated Ringer's. The osmotic effect of the dextrose in the Ringer's solution is very important since if Ringer's solution only is used to keep the urinary output at satisfactory levels serious problems with fluid overload may result. The physiological basis of this regimen is the replacement of sequestered nonfunctional extracellular fluid with balanced salt solution in order to maintain an effective circulating blood volume.¹⁶

TABLE 2. Regimen of Fluid Therapy for Aortic Surgery

	Operative	First 24 Hrs Postop	Second 24 Hrs Postop
Blood	As lost	0	0
5% Dextrose in Ringer's lactate	3-4 L*	1 L	1/2 L
5% Dextrose in water	1/2 L	2 1/2 L	2 L

* Usual infusion rate during operation—500 ml/hr

Other adjuncts such as plasma, plasma expanders, mannitol, etc. are simply not necessary.

All patients are placed in the intensive care unit for three days and are monitored continuously. Recent introduction of IPPB treatments, ultrasonic nebulization and other innovations in respiratory tract therapy has been a significant feature of postoperative care. Occasionally a simple tube gastrostomy is constructed at the time of aortic operation to facilitate respiratory care in the elderly, obese, poor-risk, or pulmonary-cripple patient.

All patients receive antibiotics prophylactically beginning the day prior to operation, continuing during operation and for three or four days postoperatively. At present the preferred antibiotic is sodium cephalothin although penicillin and tetracycline were used in past years. A topical antibiotic solution containing neomycin and bacitracin is used routinely during operation to flush the area of graft repair, the abdominal wound, and any groin incisions.

Results

Among 108 patients undergoing aortic aneurysmectomy from 1968 to 1974 there were 6 deaths related to operation, a mortality rate of 5.5% (Table 3). All deaths occurred in males. Five patients died of cardiac causes and one of pulmonary. All had one or more additional pre-existing disease. Four patients required secondary procedures. Complications requiring reoperation are a serious matter in these elderly atherosclerotic patients and may be the deciding factor tipping a borderline case into the death column.

TABLE 3. Analysis of Operative Mortality in Elective Aortic Aneurysm Surgery (1968-1974)

I.	No. of patients	108
	No. of operative deaths	6
	Operative mortality	5.5%
	Age of patients dying—66 to 85 years	
	Average 72 yrs.	
II.	Causes of operative deaths	
1.	Cardiac	5 patients
	Congestive failure	3
	Myocardial infarction	2
2.	Pulmonary	1 patient
III.	Contributing factors	
1.	Pre-existing disease	6 patients
	Cardiac	4
	Pulmonary	3
	Hypertension	3
	Renal	1
2.	Secondary operations	4 patients
	Abdominal exploration	2
	Peripheral vascular procedures	2
	Tracheostomy	2

TABLE 4. *Non-Fatal Postoperative Cardio-Pulmonary-Renal Complications*

I. Cardiac		
Pre-existing cardiac disease		43 patients
1. Congestive failure, mild	5	
2. Myocardial infarction	1	
3. Arrhythmias	4	
II. Pulmonary		
Pre-existing pulmonary disease		19 patients
1. Atelectasis, severe	7	
2. Pneumonia	2	
3. Tracheostomy required	0	
III. Renal		
Pre-existing renal disease		19 patients
1. BUN elevation	9	
Severe—>30 mgm% above preoperative level	7	
Mild—<30 mgm% above preoperative level	2	
2. Patients requiring dialysis	0	
3. Deaths from renal failure	0	

Non-fatal postoperative cardiac, pulmonary, and renal complications are listed in Table 4. In spite of a very high incidence of pre-existing disease there was a low incidence of serious complications. It should be noted that no patient died of renal failure and no patient required dialysis. Intravenous urograms are obtained routinely as part of the preoperative workup, and lumbar aortograms are performed when indicated to clarify any possible renal or renal artery problems associated with the aneurysm.

Miscellaneous complications are shown in Table 5. Only one patient, a hypertensive man, required re-operation for graft bleeding at one point in the upper aortic suture line. It is of interest to note that no patient suffered pulmonary embolism. A single patient developed deep thrombophlebitis. This occurred in a woman, the only patient requiring thigh amputation among

TABLE 5. *Miscellaneous Non-Fatal Postoperative Complications*

	Number of Patients
1. Acute cholecystitis	2
2. Upper G-I hemorrhage requiring vagotomy-pyloroplasty	1
3. Graft hemorrhage requiring re-operation	1
4. Amputations	
Among patients dying	1
Among survivors	1
5. Cerebrovascular accident	0
6. Intestinal obstruction	0
7. Wound or graft infection	0
8. Wound dehiscence	0

TABLE 6. *Operative Mortality in Elective Abdominal Aortic Aneurysm Surgery, by Chronological Eras*

	Era I 1954-61	Era II 1962-67	Era III 1968-74	Totals
Operations	53	176	108	337
Deaths	9	13	6	28
Procedure Mortality	17%	7.4%	5.5%	8.3%

the 102 survivors, and appeared in the stump of the amputated leg 49 days after the aortic operation. There was no postoperative occurrence of cerebrovascular accident, intestinal obstruction, wound or graft infection, or wound dehiscence.

Discussion

Table 6 shows the total experience with 337 elective abdominal aneurysm cases over a 20-year period, divided into three chronological eras. In Era I (1954-1961) we were attempting to remove the aneurysm *intoto* and had not adopted the lactated Ringer's regimen. In Era II (1962-1967) the Ringer's regimen was introduced, the dacron graft with dacron sutures became the standard replacement, and minimal operative dissection was employed. In Era III (1968-1974) earlier operation based on earlier diagnosis has been carried out together with refinements and innovations in all areas of clinical care. Operative mortality has progressively decreased (to 5.5%) despite increasing liberalization of indications for operation, especially in the elderly atherosclerotic with multiple-risk factors. In addition to the 337 elective cases there were 72 patients with ruptured aneurysms operated upon, having an operative survival rate of 48.6%.

Although in Eras I and II operative deaths were predominantly cardiac and pulmonary in origin, we also lost patients from intestinal gangrene, anastomotic leaks, and renal failure, causes largely technical in nature or related to improper fluid management.²⁰ Deaths from these causes did not occur in Era III.

Table 7 lists the operative mortality for elective aneurysm repair taken from several representative series in the recent literature. Obviously, all report improvement with increasing experience. Mortality rates for the most recent series reported a range from zero to 9.8%, with a mean of about 5%. No doubt these figures could be improved in many instances by more stringent selection criteria. However, the fate of those judged unfit for operation is such that the latter approach does not seem proper.¹⁹ In fact, indications for operation have been increased rather than reduced. An operative mortality rate in the range of 3 to 7% appears to be reasonable and acceptable for these patients.

Several studies^{2,6,8,18,19} have compared the long-term survival rates of patients with untreated aortic aneurysms

TABLE 7. *Recent Operative Mortality for Elective Aortic Aneurysm Repair—Selected Reports from the Literature*

Year	Author	No. of Patients	Operative Mortality
1964	DeBakey et al. ⁶ (Total series-1952-64)	1719	8%
	(Recent series-1962-64)	533	5%
1966	Szilagyi et al. ¹⁸	127	6.3%
1968	May et al. ¹⁴	135	9.8%
1970	Baker et al. ³ (Total series-1953-69)	390	6.6%
	(Recent series-1966-69)	150	2.7%
1972	Ameli et al. ¹ (Total series-1955-71)	714	9.7%
	(Recent series-1970-71)	162	6.7%
1972	Malan et al. ¹³	154	9.1%
1973	Key and Sokol ¹¹	146	0
1973	Stokes and Butcher ¹⁷	87	3.4%
1974	Present series (Total-1954-74)	337	8.3%
	(Recent-1968-74)	108	5.5%

with those of patients undergoing surgical resection and graft replacement. All are in substantial agreement that elective surgery prolongs life expectancy. Patients with untreated aortic aneurysms have a very poor outlook. Almost half die during the first year following diagnosis, about 80% are dead at 5 years and all are dead at 10 years. The principal cause of death is rupture of the aneurysm. By contrast, of those operated upon, about 20% die during the first postoperative year, 50% are dead at 5 years, while about 25% are still alive at 10 years. The chief cause of death in the operated group after 10 years is cardiac disease.

Since surgical therapy can be shown to increase life expectancy in patients with aortic aneurysms, and fatal rupture can be prevented by elective resection, it is important, therefore, that diagnosis be made and definitive therapy carried out before this catastrophic event occurs. Likewise, it is imperative that operative mortality and morbidity be at the lowest possible levels if maximum benefit is to accrue from surgical management, since the

limiting factors of coronary disease and other complications of atherosclerosis are still operative after aneurysm removal. It has already been noted above that mortality and morbidity rates related to operation have become progressively lower during the 23 years since Dubost's original operation. The important factors influencing this trend will be discussed below.

Earlier Diagnosis Using Non-invasive Techniques

The important advances noted above are the B-mode ultrasonic scan and the radionuclide aortogram. More widespread application of the sonogram as a screening method in patients with known atherosclerosis should reveal an increasing number of unsuspected aneurysms, both large and small.

Refinements in Operative Technique

These refinements include minimal dissection, reduced blood loss, heparin to prevent arterial and venous thrombosis, and the special maneuvers listed above under surgical management (Figs. 2-6). Refinements in anesthesia techniques, the use of new and safer anesthetic agents, and the constant intra-operative monitoring by the anesthesiologist of arterial and central-venous pressures and blood gases have also been of the utmost importance.

Improvement in Fluid Management

The proper use of the regimen based on lactated Ringer's solution has continued to prevent the hypotensive and renal complications of aortic surgery.¹⁶ Guidelines for this regimen include satisfactory blood pressure levels and urinary output without vasopressors, blood replacement as lost, age and size of the patient, preoperative state of hydration, prior diuretic and hypertensive medications, pulmonary and cardiac status, duration and magnitude of operation, and any unusual extrarenal losses.²⁰

TABLE 8. *Unusual Manifestations of Aortic Aneurysms*

I.	Renal artery problems
	1. Multiple, arising from aneurysm
	2. Stenosis at origin
II.	Renal vein variations
	1. Retroaortic
	2. Low-lying left vein
	3. Circumaortic collar
III.	Vena Cava problems
	1. Double vena cava
	2. Left-sided cava
	3. Aorto-caval fistula
IV.	Horseshoe kidney
V.	Mesenteric artery problems
	"Meandering mesenteric"
VI.	Inflammatory aneurysm

Innovations in Cardiac and Pulmonary Therapy

Routine use of the intensive-care unit postoperatively with constant monitoring and the application of any necessary cardiac resuscitative measures and routine pulmonary therapy with ever improving technology have been major factors enabling surgeons to operate successfully on many patients with aneurysm who otherwise could not survive the operative procedure. We believe the routine use of antibiotics prophylactically is important in preventing pneumonitis as well as urinary tract, artery graft, and wound infections.

Recognition and Handling of Unusual Manifestations

A number of unusual manifestations of abdominal aneurysm have been observed and recorded. Table 8 lists the more common ones. Awareness of these problems, recognition at the time of operation, and proper handling are imperative if such catastrophic complications as massive hemorrhage, loss of a kidney, or intestinal gangrene are to be averted. Management of horseshoe kidney depends on the origin of the blood supply to the renal tissue. Appropriate methods of managing all these special problems have been reported^{5,9,10} and have undoubtedly resulted in reduced morbidity.

Thus advances in all areas of clinical management have lowered the operative mortality to acceptable levels. While technical refinements may continue to occur to some degree, further improvement in mortality will most likely be dependent on earlier diagnosis with operation on smaller lesions, since the latter carry lower complication rates. At the same time, liberalization of indications for operation in the elderly patient with multiple risk factors tends to offset this trend and will keep the operative mortality at a certain irreducible minimum.

In view of the present-day acceptable surgical risk coupled with the lethal nature of untreated aneurysmal disease, it appears that an aggressive surgical approach is justified. The guiding premise is that most patients with unruptured abdominal aneurysms regardless of age should be candidates for elective surgical repair, unless other associated conditions make the contraindications to operation overwhelming. Such conditions, either cardiac, cerebrovascular, renal, pulmonary or malignant disease, render the operative risk unreasonable or impose an obligatory limitation on life expectancy of less than two or three years.

The small aneurysm (less than 6 cm) presents a special situation. Since recent studies^{18,19} have revealed a significant incidence (20%) of unexpected rupture of these small lesions, the usual patient without contraindications should be offered operation. Another special problem is the elderly patient over the age of 75 with an aneurysm. If the lesion is large (greater than 6 cm) and the patient a reasonable risk, operation appears indicated. If the aneurysm is small and the patient has a limited outlook,

he should not be operated upon. For the very elderly, over the age of 80, operation probably should not be recommended unless the patient is physiologically younger than his chronological age, has a large or symptomatic aneurysm, is a suitable operative risk, and otherwise has a useful life expectancy of two or three years. Careful surgical judgment is necessary in these special cases to render a judicious decision regarding operation.

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DISCUSSION

DR. GEORGE JOHNSON, JR. (Chapel Hill, North Carolina): Dr. Thompson has emphasized the low mortality with elective repair of abdominal aortic aneurysms. As he has also emphasized, another important consideration in these patients with multisystem arteriosclerosis is the longevity following the operation. It would seem that the frequently associated cardiac, renal, and cerebral vascular diseases would cause early death in many of these patients who survive the operation for aneurysm.

(Slide) One-hundred fifteen patients who survived the repair of an abdominal aortic aneurysm at the Northfile Memorial Hospital have recently been reviewed, using the life table analysis method. It is predicted that 58% of these patients, with an average age of 65, will survive eight years. The survival of the general population the same age, using recent data from the Metropolitan Life Insurance Company, is 76%, not too different from the patients who survive repair of an abdominal aortic aneurysm. With the low current operative mortality reported by Dr. Thompson, the continued aggressive approach to the patient with an aneurysm of the abdominal aorta seems warranted.

DR. DONALD SILVER (Durham, North Carolina): It is always very difficult to add or change anything in Dr. Thompson's presentations because they are always so complete. However, I would suggest that because of the importance of adequate fluid replacement, we frequently start our intravenous infusions the night before. We have found that our patients sleep quite well and have no problems from the infusions. Since we have been hydrating our patients in this manner, we have not had any problems with postoperative renal failure.

The second suggestion concerns the way we handle the patient with profound pulmonary insufficiency. In the past, some of these patients have been refused surgery, but the poor prognosis associated with large aneurysms compels one to operate upon the aneurysm while "protecting" the respiratory system. In the last couple of years we have begun using continuous epidural anesthesia on patients with aneurysms and profound pulmonary insufficiency. The epidural anesthesia, which may

be supplemented by mask or endotracheal anesthesia, provides good relaxation. By leaving the catheter in place for one to three or four days postoperatively, pain is relieved, and the patients breathe and cough well and have fewer pulmonary problems. We have successfully operated upon patients with this type of anesthesia who have had resting pO_2 's in the 40 mm/Hg range and maximum breathing capacities of 30–40%.

DR. LARRY H. HOLLIER (Closing discussion): Dr. Johnson, we would agree with you that the deaths in the unoperated aneurysms are primarily due to rupture, and that by operating on these earlier we eliminate this factor in the mortality. I think it is probably well established at this point in time that the resection of aneurysms has contributed to the survival of patients with this disease.

Dr. Silver, we thank you for your comments, and appreciate greatly your suggestions.

In closing this discussion I think it is appropriate to again mention something about indications for surgery. Particularly, we might wonder about the borderline cases. Even small aneurysms less than 6 cm in size, as Dr. Szilagyi has shown, have a significant, 20 percent incidence of unexpected rupture. These patients with small aneurysms, without contraindications, we feel should be offered operation.

Likewise, in the elderly patients, over the age of 75, with a large or symptomatic aneurysm, operation appears indicated if the patient is physiologically younger than his chronological age, he is a suitable operative risk and otherwise has a useful life expectancy of several years.

In summarizing these indications, we feel that because of the lethal nature of untreated aneurysmal disease an aggressive surgical approach is justified, regardless of the size of the aneurysm or age of the patient. This approach must, obviously, be modified when associated medical conditions or malignant disease render the operative risk unreasonable or impose an obligatory limitation on life expectancy of less than two or three years. It is in these borderline cases, of course, where careful surgical judgment becomes the art, and is no longer merely the science, of surgery.

Stenotic and Obstructive Lesions in Acute Dissecting Thoracic Aortic Aneurysms

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The present study of 33 operatively treated patients, 88 per cent of whom survived the procedure, is concerned with an important problem associated with acute thoracic aortic dissection, the stenotic and obstructive lesions of the aorta and its branches. Their variety and nature are described, as are the additional operative procedures deemed necessary at the time of the operation, immediately thereafter, or later on. Much has been learned about these difficulties from clinical and autopsy observations and especially from careful arteriographic surveys. They seem to be generally well withstood following resectional and grafting procedures upon the affected segment of the thoracic aorta. Occasionally, additional operative manipulations may be necessary at the same time, for example, interpolation of grafts between the ascending aortic graft and a coronary when the origin of the latter is sheared off by the dissection, and distal arterial manipulations when the patient still has ischemic lower extremities immediately after the primary procedure. Later operations must sometimes be performed because of persistence of complaints such as intermittent claudication. It is extremely rare that immediate reoperation is advisable because of indications of intra-abdominal ischemia. Much more can be learned from careful pre- and postoperative arteriographic study.

IT is now well established that acute and subacute dissecting aneurysms of the thoracic aorta and chronic aneurysms of similar type can be managed operatively with good immediate results.¹⁰ The hospital survival rate following the last 43 operations* was 88% in the acute and subacute and 90% in the chronic cases (Table 1). It has also become clear from this experience that the aortic insufficiency which so often develops in acute dissection can be treated effectively by resuspending the flail valve during the resection and grafting procedure. In contrast,

valve replacement is required for long standing regurgitation associated with chronic aneurysms. In addition, patients seem to do relatively well after operation, considering the widespread nature of the arterial involvement and the frequent co-existence of other bothersome and life-threatening diseases such as hypertension, generalized arteriosclerosis, coronary sclerosis, myocardial infarction, hypertensive and other heart disorders, diabetes, obstructive or restrictive lung disease, nephrosclerosis, renal calculi, prostatic obstruction, etc.

One important aspect of the problem which has received little attention in reported studies deals with the accompanying interference with blood flow through the aorta and its important branches. It is with this matter that this report is concerned. It is our purpose to analyze the available relevant data from 33 acute and subacute cases, attempting to point out the frequency with which stenotic and obstructive arterial lesions occur, the observable consequences, or the absence of any noticeable effects, the results achieved by resection and grafting of the appropriate aortic segment, the occasional necessity of immediate additional operative manipulations, or of later arterial reconstructive procedures, and the need for further study of this entire matter.

As has been true in other series most of the patients treated during the early part of the period covered by this survey were studied by forward aortography. This technique frequently demonstrated the thoracic aorta only. When the abdominal segment was visualized the aorta and its branches were usually not delineated in a clean-cut manner. A few investigations were done by cardiac catheterization and cineangiography and only the thoracic aorta and its branches were surveyed. In contrast, the more recent cases have had excellent angiographic demonstration of the entire aorta by the retrograde catheter technique except in those few instances in which

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*These are personal cases of the senior author treated during the past 11½ years at the Indiana University Medical Center and by him and his associates at St. Vincent Hospital. In one exceptional case, one of our patients some time after undergoing resection and grafting of the descending aorta suffered a second separate dissection several centimeters distal to the graft. This episode was managed successfully by our colleague, Dr. H. King.

TABLE 1. *Hospital Survival in Per Cent*

Site of Aortic Wall Tear or of Chronic Aneurysm	Number of Operations	Hospital Survival
Ascending aorta*	16	100
Descending aorta**	14	79
Arch	1	100
<i>Acute Dissection in Old Chronic Aneurysm</i>		
Descending aorta	2	50
<i>All Acute and Subacute Dissections</i>		
	33	88
<i>Chronic Aneurysms</i>		
Ascending aorta***	9	89
Descending aorta	10	100
All	10	90

*In one case the tear was incorrectly localized and the descending aorta was resected and replaced with a graft. Thirteen had acute aortic insufficiency and underwent valve re-suspension.

**In two cases the tear was incorrectly localized and the ascending aorta was replaced with a graft.

***All had massive aortic regurgitation and underwent valve replacement.

the initial films clearly showed no dissection beyond the arch or mid-descending aorta. Those in which visualization of the abdominal aorta was obviously unnecessary and the earlier cases in which such studies were omitted, because of the technique used or were inadequate in detail, reduced the numbers in which the changes in the abdominal aortic segment and its branches could be properly analyzed. Our patients have also had too infrequently followup arteriograms and assessment of hepatic, renal and gastrointestinal function, such studies generally having been carried out only when they seemed indicated because of complaints or relevant findings on physical or ordinary roentgenographic examination. Despite these limitations some interesting observations have been forthcoming.

Extent of involvement. As well as it was possible to determine from arteriographic studies, operative findings, and post mortem examinations, the dissection was generally quite diffuse (Table 2). Indeed, in only two instances was the dissection limited to that segment of the aorta in which the tear occurred. In at least 23 cases (70%) it extended well into the abdominal aorta or even beyond into the iliac arteries.

Narrowing of the aortic lumen. Very commonly the

TABLE 2. *Extent of Dissection*

Site of Aortic Tear	Number	Extent of Dissection (Number)
Ascending aorta	16	Ascending aorta (1)
		Arch (3)
		Descending aorta (4)
		Abdominal aorta (8)
Arch	1	Descending aorta (1)
Descending aorta	16	Descending aorta (1)
		Abdominal aorta (15)

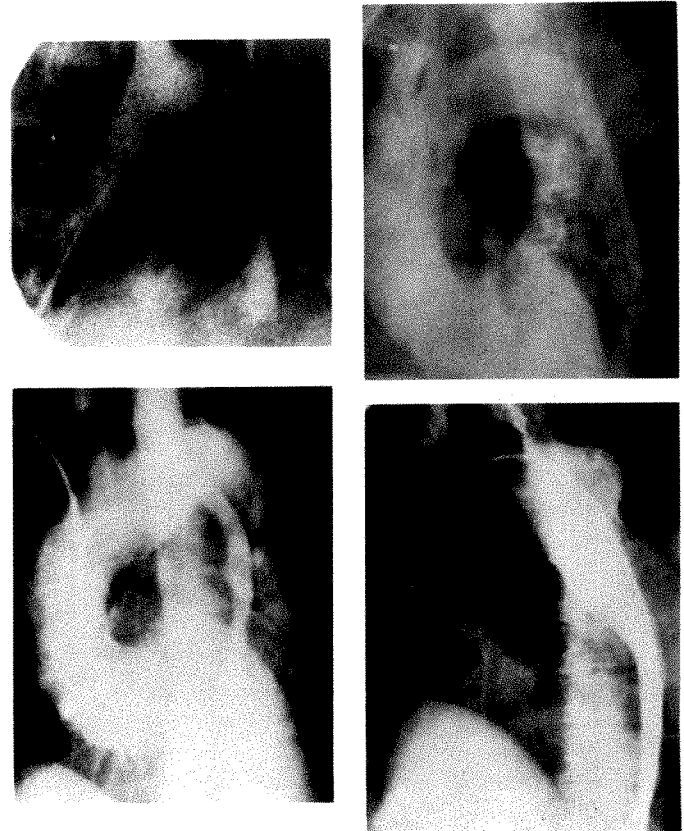


FIG. 1. Photographs illustrating extreme narrowing of aortic lumen. Upper left, frame from cineangiogram of 38-year-old woman; upper right, forward aortogram in 58-year-old man; lower left, forward aortogram in 69-year-old man and lower right, retrograde study in 60-year-old man.

extraluminal dissection compressed the true aortic pathway markedly. In some cases the diameter of the lumen was only from one to one and a half centimeters. Four examples are illustrated in Fig. 1. Three of these patients survived. The 69-year-old man died 20 days postoperatively of an acute coronary thrombosis. This was the only hospital death among those cases illustrated in Figure 1 and other figures. He also suffered from tubular renal necrosis. The degree of luminal narrowing was truly remarkable in a young lady of 38 with subacute dissection of the ascending aorta. Four months prior to operative treatment she developed suddenly severe chest pain associated with mild aortic insufficiency, an enlarging heart and progressively severe heart failure. She apparently underwent a second dissection 3 months and a third one month before operation. She was then in profound left heart failure, had a gallop rhythm, marked cardiac and ascending aortic enlargement, mild aortic regurgitation and elevated left ventricular and wedge pressures (30 and 33 mm Hg at rest, respectively). Her coronary arteries appeared normal. The aortic lumen was only a few millimeters in diameter and was actually no larger than that of the right main coronary artery. Surprisingly enough,

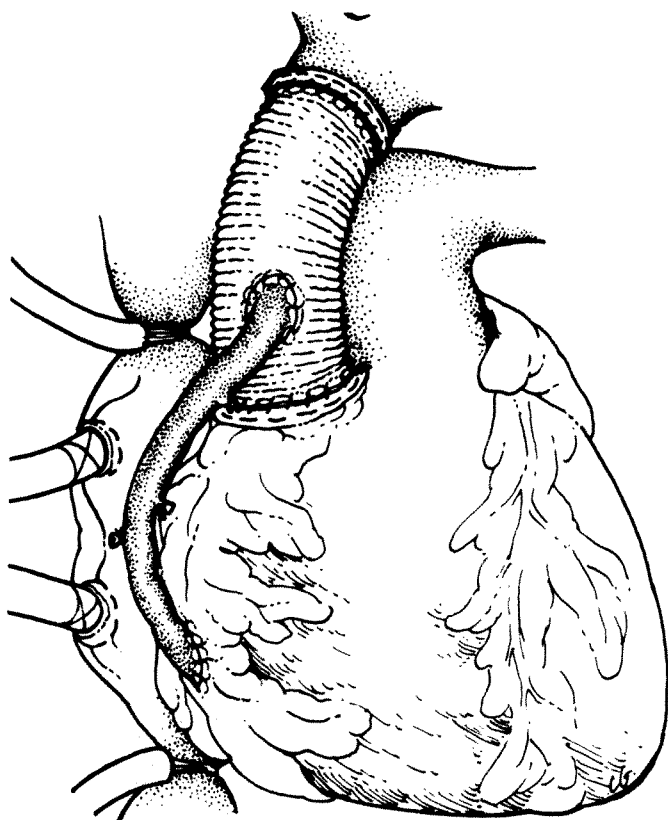


FIG. 2. Drawing illustrating bypass graft between aortic graft and distal right main coronary artery.

no gradient could be measured across the constricted aortic segment. Since the mechanism of the cardiac dysfunction was obscure, consideration was given to her having some poorly understood myopathy or to Marfan's involvement of terminal coronary branches as an explanation for her profound failure. Following resection of the aorta, resuspension of the aortic valve, and insertion of an aortic graft, her cardiac status improved dramatically. The gallop eventually disappeared, the heart became smaller, and she became essentially symptom free. Unfortunately, 10½ months postoperatively she developed severe pain and marked expansion of the false lumen in the region of the arch. She expired of bleeding from a peculiar intravascular coagulopathy immediately following an otherwise successful resection and grafting procedure, the only death from a secondary operation necessary because of the patient's intrinsic arterial disease or its operative treatment.

Coronary artery disruption. In one 51-year-old man who was said to have had an aortic diastolic murmur for several years without significant regurgitation but who had marked valvular insufficiency on admission a few hours after onset of his acute dissection, the arteriograms revealed poor opacification of the right coronary. At operation it was found to have been sheared off by the dissection which extended deeply into the sinuses of Valsalva, though it spared the area of origin of the left coronary. After resection and grafting of the ascending

aorta and careful suspension of the valve, it was necessary to interpolate a saphenous graft between the aortic graft and the distal main right coronary beyond an area of heavy arteriosclerotic involvement before it was possible to dispense with cardiopulmonary bypass (Fig. 2). The patient has done well. In all the other cases, no matter how extensive the proximal dissection into the sinus areas, the integrity of aortic-coronary continuity was maintained.

Cerebral manifestations. On admission a few patients exhibited varying degrees of cerebral involvement, presumably as the consequence of interference with blood flow to the brain. It is possible that in rare instances such symptoms may have resulted from the marked hypotensive episode which occasionally is noted with the onset of dissection, or from an acute hypertensive encephalopathy. It seems clear, however, that generally it was due to involvement of the arch branch vessels which vascularize the brain. In all cases in which the dissection extended from the ascending aorta into the arch there was angiographic evidence of some narrowing, at times rather marked, of the innominate artery and sometimes of the left carotid and left subclavian as well. Furthermore, in almost all patients in whom the tear began in the ascending aorta the pulses were weaker in the right upper extremity than the left and in all of them in whom the blood pressure was measured in the two extremities it was found to be substantially lower in the right. The differences were as great as 90/60 and 170/70, the average being 100/53 in the right and 155/65 in the left. In one 54-year-old lady obtunded to the point of deep stupor the right carotid and all the pulses in the right upper extremity were palpably weaker than those on the left and the arteriograms showed substantial narrowing of the innominate and only faint opacification of the left carotid and subclavian arteries. Her cerebral status gradually returned to normal after resection of the ascending aorta, resuspension of the valve, and insertion of a graft. Two years following operation she underwent a successful repair of a previously unrecognized atrial septal defect, now associated with profound cardiac failure. In her case and in that of two other patients, the pressure in the right arm has remained lower than in the left. In one instance the pressure was actually a little lower in the left than in the right arm and in the others it became equal in the two.

Blood pressures were not commonly measured in both upper extremities in those instances in which the process began in the descending thoracic aorta. In general, however, no difference in the pulses or pressure in the two extremities was noted despite the fact that angiographically the dissection frequently involved the left subclavian and in two cases extended in a retrograde fashion all the way across to the root of the aorta.

Ischemia of the lower extremities. This observation was noted in 4 of the 16 patients in whom the tear in the aortic wall occurred in the ascending aorta or arch. This constituted half of those in whom the dissection was

TABLE 3. *Lower Extremity Ischemia on Admission or Upon Completion of Primary Operation*

Site of Aortic Tear and Graft	Age	Limbs Involved	Method of Treatment and Interval Between Primary and Secondary Procedures.	Result
Ascending aorta	54	Left	None	Good circulation immediately after initial operation. No further trouble. Good pulses.
Ascending aorta	24	Right initially. Left after use for c-p bypass.	Fogarty balloon manipulation immediately after primary operation. No thrombi recovered.	Good pulses. Residual ischemic paralysis right foot necessitating footdrop brace.
Ascending aorta	36	Left initially. Right also after use for c-p bypass.	Fogarty balloon manipulation immediately after primary operation. Thrombi recovered.	Good pulses. No symptoms.
Ascending aorta (Figs. 3 & 4)	32	Both	Resection infrarenal aorta with proximal fenestration and closure false passage distally 6 weeks after initial operation.	Limbs became viable after primary operation but still pulseless and with residual weakness and hypesthesia left foot. No symptoms and good pulses after second operation.
Descending aorta (Fig. 5)	57	Right	Resection infrarenal aorta and proximal common iliacs. Aortic graft to united common iliacs. Eight months after primary operation.	Barely viable on admission, better after primary operation. Severe claudication. Improved after second operation but persistent claudication. Pulses present but not normal.

known to extend into the abdominal aorta or beyond. Such ischemia was present in only one of the 16 in whom the dissection began in the descending thoracic aorta even though the abdominal segment was involved in all but one. All of the painful and hypesthetic or anesthetic limbs had absent pulses (Table 3). One limb, markedly ischemic on admission, exhibited satisfactory restoration of circulation and pulses immediately after the aortic resection. In two patients bilateral Fogarty balloon manipulations immediately after the primary operation brought about return of good pulses in all limbs, though one patient had sustained such ischemic nerve damage that he had to wear a footdrop brace. In one of these two patients no thrombi were recovered by the passage of the catheter, while in the other some thrombi were removed.

Two men required aortic reconstructive procedures 6 weeks and 8 months after the original operation because of incapacitating intermittent claudication. The result in one was excellent. The less than perfect outcome in the other was very likely the result of proximal aortic narrowing from organized clot in the extraluminal passage and from fairly severe associated arteriosclerotic disease. In the former the dissection had markedly obstructed the infrarenal aorta (Fig. 3 and 4). The retrograde aortographic study revealed no opacification of the superior mesenteric artery from the true lumen nor was there evidence that the celiac axis was connected with it. Furthermore, the left renal artery arose from the false passage. The operation consisted of resection of the infrarenal aorta with proximal fenestration, secure approx-

imation of the coats of the aorta distally, and insertion of an aortic graft. In the other case (Fig. 5) there was an old clot in the false passage which narrowed the aorta and obstructed one iliac artery. Both renals arose from the true lumen. The aorta was transected below the origin of the renal arteries, the false passage closed off, the rest of the aorta resected, the mesial portions of the common iliacs approximated, and a straight aortic graft interpolated.

Abdominal Visceral Branch Involvement. Aortograms adequate for interpretation of visceral involvement were available in 8 of the 23 cases in which the dissection extended into the abdominal segment or beyond. In analyzing them, we have omitted consideration of the intercostals, lumbar and lumbosacral arteries and the inferior mesenteric. We have concentrated, instead, upon the major branches, the celiac axis, the superior mesenteric artery, and the renals. Either on the original or later studies all 4 of these major trunks opacified normally in only 3 cases. One or more major branches were not visualized as coming off the true aortic pathway in the others (Table 4). In two the flow into one major branch did not come from the true lumen (Fig. 6). In one the flow into two branches (Fig. 7) did not come from the lumen and in two it appeared that only a single renal artery arose from the true aortic pathway (Fig. 8). In one of the latter, a 46-year-old man the original retrograde study revealed opacification of the right renal from the true channel and the origin of the visualized branches of the celiac axis could not be determined with certainty. In

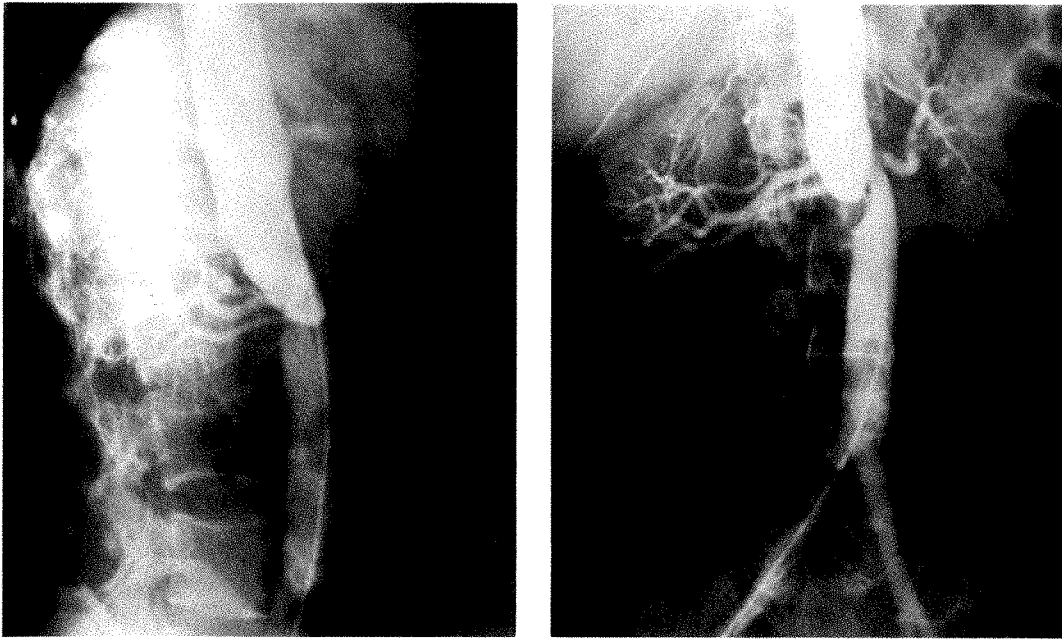


FIG. 3. Aortograms showing near total obstruction of the infrarenal aorta, origin of left renal from false channel, failure of opacification of superior mesenteric and celiac axis.

a postoperative study two months later both true and false pathways were simultaneously demonstrated and the celiac axis, superior mesenteric, and left renal arteries were seen to arise from the false lumen.

In some instances it was clear that the branches not communicating with the true lumen received adequate flow from the false channel, signifying persistence or development of union of the two passages beyond the distal end of the graft where it was attached to the carefully united coats of the aorta. None of these patients had clinical evidence of hepatic or intestinal ischemia, or renal dysfunction. Those with origin of a renal artery from the false channel had generally good pyelographic and nephrographic studies, though in one instance (Fig. 3) the ipsilateral nephrogram was less densely delineated than the other. Furthermore, one patient previously mentioned, whose arteriograms did not include an abdominal

aortic study and who died 20 days postoperatively, was shown at autopsy to have one renal artery completely occluded by the dissection, the other 75% narrowed. However, abdominal visceral ischemia in these cases seemed sufficiently rare to make it generally inadvisable to add a second major operation of questionable outcome to the primary procedure in an effort to attempt to reconnect branch arteries and the true lumen.

Discussion

It has been known for some time that acute and sub-acute thoracic aortic dissection may be accompanied by narrowing of the aortic pathway and stenosis or obstruction of branch arteries and that these alterations may result in disturbances of blood flow, diminished or absent pulses, cardiac, neurologic, abdominal, and renal problems. Most of the earlier contributions were based upon

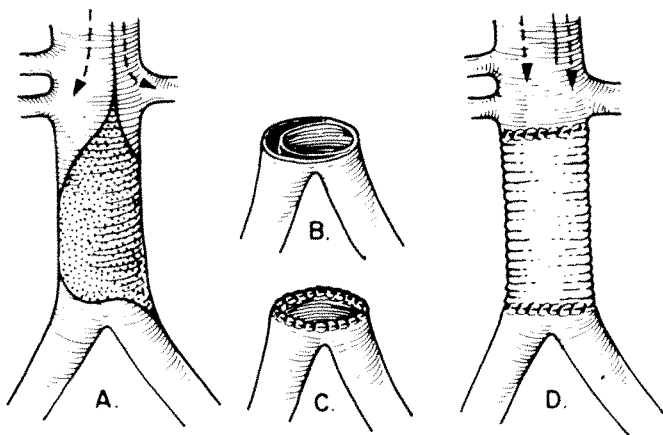


FIG. 4. Drawings illustrating operative procedure performed.

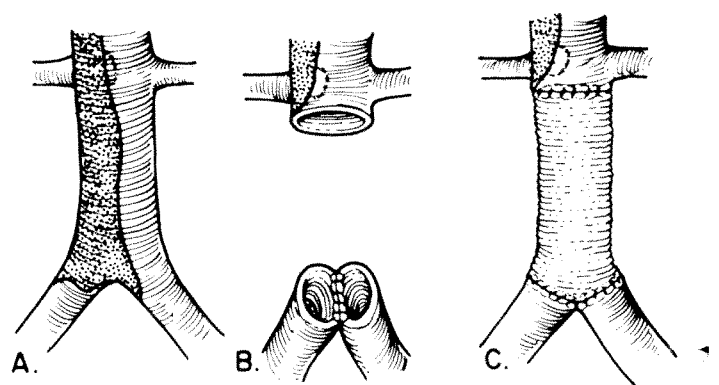


FIG. 5. Drawings indicating condition found at operation 8 months after original thoracic aortic resection and reconstructive procedure carried out.

TABLE 4. *Involvement of Abdominal Visceral Branches*

Branches Not Opacified From True Aortic Lumen	Age of Patient	Comment
Left renal, Celiac, Superior mesenteric (Fig. 3)	32	Left nephrogram less dense than right
Left renal, Celiac, Superior mesenteric (Fig. 8)	46	Later postop study shows filling of all from the two separate channels
Left renal (Fig. 6)	60	Origin left renal from false passage proved at later operation for aneurysmectomy. Good pyelogram and nephrogram
Superior mesenteric	37	On original study and others about 9 months and 2 years later
Right renal, Superior mesenteric (Fig. 7)	54	

clinical and autopsy findings, particularly the latter.^{2,6,8} Insight into these associated difficulties in living patients awaited the use of angiographic techniques in such cases.^{3,5}

As was true in the patients we have reviewed, most patients at first were examined by forward aortography. Such studies were often limited to the thoracic segment. When they included the abdominal aorta as well they were often characterized by delineation too poor for careful analysis of branch artery involvement, communication of false and true channels, etc. Many surgeons and internists feared, as we did, that the retrograde catheter technique might prove hazardous, that the catheter tip might pass into the false passage, perforate its thin wall and result in exsanguinating hemorrhage. Indeed, such accidents occurred, though apparently rarely. Yet it seems clear that this technique, now used quite frequently in cases of dissecting aneurysms, has been proven safe. Careful identification of the position of the end of the catheter by appropriate test injections of small amounts of contrast material before delivering a large bolus under pressure has largely eliminated any real hazard. It certainly has the advantage of more precise arteriographic visualization and of permitting examination of the entire aorta and its branches when a more limited study is not entirely adequate. The principal defect in current methods is the failure in a few instances to identify the precise point of the aortic wall tear, a matter of utmost importance to the surgeon in selecting the proper operative approach.

Most of the recent clinical reports have concerned themselves with methods of management, medical or operative, or a combination of the two. Quite a few of the later studies have been limited largely to some specific problem, such as renal artery involvement.^{4,9,11-13} Analysis of our personal cases points to the need not only for careful, detailed, and comprehensive preoperative

studies, but for more postoperative examinations in properly selected cases.

In this study we have not considered those rare cases in which the dissection begins not in the thoracic aorta but elsewhere, such as the carotid, the renal artery, the distal abdominal aorta, etc.

The effect of proper resectional and grafting operations upon that portion of the thoracic aorta in which the aortic wall tear occurs often has a remarkable effect upon blood

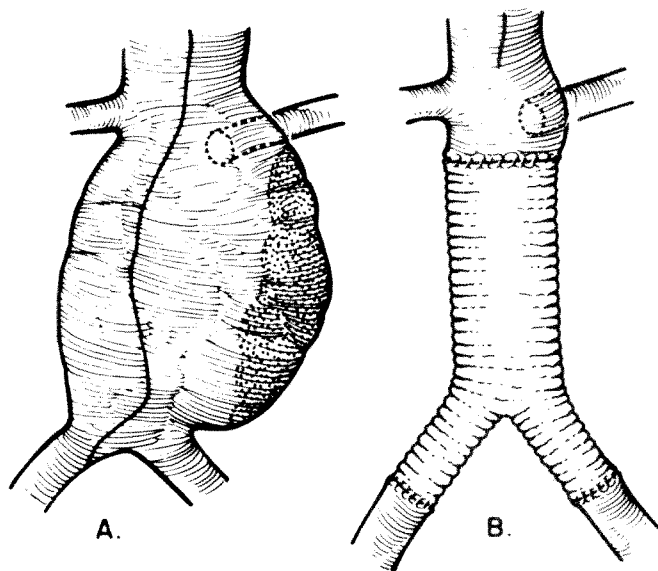
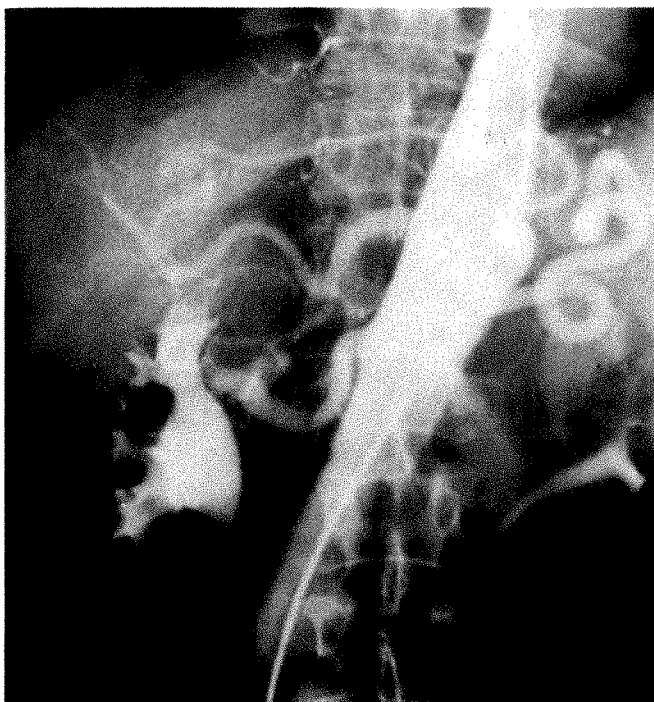


FIG. 6. Retrograde aortogram in 61-year-old man 18 months after original thoracic aortic resection and grafting procedure showing no demonstrable left renal artery but a good pyelogram. Other exposures showed good bilateral nephrograms and some opacification of the aneurysm which contained a large thrombus. Drawings of findings at operation indicating origin of left renal from the false channel, and the operative procedure carried out.

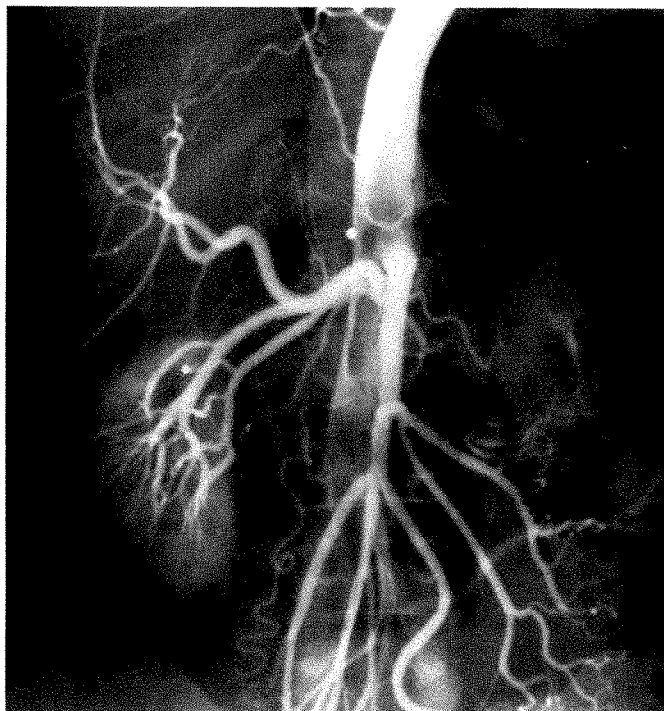


FIG. 7. Aortogram in 54-year-old woman showing opacification of right renal and superior mesenteric from false channel.

flow. The rapid improvement in the mental status of some of our patients was almost surely such a consequence. In several instances ischemic limbs had full restoration of pulses and circulation, while in others marked improvement was noted. Rather astonishing improvement in renal function has been described, as in the case of Mulder and Kaufman.⁹ Remarkably enough, resection and grafting of the affected descending thoracic aorta was followed in Steiner and Wexler's case of renal arteriovenous fistula by disappearance of the abdominal

bruit!¹² Yet satisfactory return of circulation does not invariably occur. Two of our patients with ischemic limbs required immediate transfemoral Fogarty balloon manipulations while in two others later aortic and aorticoiliac reconstructive procedures were necessary because of residual circulatory difficulties. We have already referred to one fatal case in which post mortem examination revealed total occlusion of one renal artery and 75% narrowing of the other. Forty years ago Kennedy described a patient with abdominal and back pain associated with melena whose autopsy revealed dissection of the superior mesenteric artery associated with thrombosis and extensive infarction of most of the small intestine and the right and transverse colon.⁷ Obviously, a previously functional coronary artery disconnected from the aorta by the acute dissection requires restoration of pulsatile blood flow by means of a grafting procedure as was the case in one of our patients. Nevertheless, it would appear inadvisable to attempt direct coronary arteriography in acute and subacute cases since such manipulations would not only prolong the preoperative studies but would almost surely prove hazardous. Furthermore, such a difficulty might be suspected from the ordinary aortic flush aortograms and, under any circumstances, would be evident at the time of operation. Fortunately, in most instances despite extensive dissection deep down into the region of the sinuses of Valsalva the areas of origin of the two coronary arteries seem to withstand such injury.

Judging from our experiences and those reported, disastrous consequences from involvement of the abdominal visceral branches apparently occur very rarely. Consequently, it would certainly seem inadvisable to carry out abdominal exploration immediately following the primary thoracic operation simply on the basis of arteriographic evidence of failure of opacification of main



FIG. 8. Pre- and postoperative arteriographic study in 46-year-old man showing in the former opacification of right renal from the true channel and in the latter the false lumen as well giving origin to the celiac axis, superior mesenteric and left renal arteries.

visceral arteries from the true aortic pathway. Undoubtedly, a case may be encountered in which there will be present shortly after operation such clear-cut signs of life-threatening intra-abdominal ischemia as to make necessary immediate abdominal exploration.

Additional good arteriographic studies, both before and after operation, should help clarify the various mechanisms relating to the interference of blood flow into branch arteries. Certainly in some cases the true lumen of the artery is significantly narrowed by the dissection itself. It is also clear that in some unusual instances a tear in the separated inner coat may produce a flap-like obstruction or stenosis. If the narrowing of the true pathway is great enough, thrombosis at this site or distal to it may occur and such thrombi may result in embolism to more distal portions of the arterial tree.¹ Small thrombi were recovered both from proximal and distal segments in one of our patients whose lower extremity ischemia made necessary transfemoral Fogarty catheter balloon manipulation. In the other similar case no thrombus at all was found, yet adequate restoration of circulation and good pulses was achieved by this procedure. One may speculate that the good result obtained in cases such as this is accomplished simply by balloon compression of the thrombus in the extraluminal passage in such a manner that it becomes more evenly distributed with resultant increase in the effective cross sectional area of the true pathway.

The general improvement in flow through affected branches that follows the primary thoracic resectional and grafting procedure certainly deserves more study. One mechanism responsible for this beneficial result may be the decrease in pressure in the false channel resulting from the careful approximation of the two coats where the distal end of the graft is attached. The improved situation may be related to the phenomenon of re-entry or distal communication of the false and true aortic pathways for it is not known how often this exists prior to the primary thoracic operative procedure or immediately afterwards. Certainly the direct communication of the two aortic channels distal to the site of the graft must be an important factor in the maintenance of adequate blood flow through branches no longer arising directly from the true lumen and in the adequate nutrition of the tissues they supply. It is equally clear that in certain cases the blood in the extraluminal passage becomes clotted and later organized. This would appear to happen most commonly when no re-entry has taken place and the two passages have remained separate beyond the intrathoracic grafted area.

When patients recover from the initial operation with viable limbs but with obvious impairment of circulation it seems wise to defer reconstructive arterial procedures until a somewhat later date, allowing the patient an opportunity to recover well from his first procedure. This is the policy we followed in two of our patients. Undoubt-

edly secondary operation will also be judged advisable, as was true in two of ours, in patients who later develop marked aneurysmal dilatation of the original false channel either in the chest or abdomen. If the coats of the aorta are intact proximally and distally or if they can be united without interfering with blood flow into branch arteries prior to insertion of the graft, this is an ideal situation. If, however, preservation of flow into an important branch depends upon keeping the false channel open proximally, it is necessary to deal with this end by fenestration instead.

Stenotic and obstructive lesions of the aorta and its important branches constitute an important part of the general process of acute and subacute dissecting aneurysms of the thoracic aorta. Much has been learned about them from clinical observations, from post mortem examinations, and especially from arteriographic studies. Certain important features associated with these lesions are incompletely understood. In general, they can be managed satisfactorily by proper prompt operative procedures upon the affected segment of the thoracic aorta followed in a few unusual cases by additional operative manipulations at the time of operation or immediately after it is completed. In a few others such involvement will result in problems which will require later reconstructive operations. Altogether, patients who receive proper treatment initially get along surprisingly well despite these associated difficulties.

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New Technique for Construction of Composite Dacron Vein Grafts For Femoro-Distal Popliteal Bypass in the Severely Ischemic Leg

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Vascular surgeons are in agreement that autogenous saphenous veins are best suited for bypasses from the common femoral artery to the distal popliteal artery in the management of femoropopliteal occlusive disease associated with the severely ischemic foot. Such a graft should be of adequate size (more than 3 mm in diameter) throughout its length for a successful outcome. In some patients the vein is of good size for 15 or 20 cm then branches into several small veins. Reports by most surgeons are unfavorable concerning the use of prostheses and bovine heterografts for anastomosis to the distal popliteal artery or to one of its branches. Our experience with composite dacron vein graft bypasses employing a fluted end-to-end anastomosis had been unfavorable and was similar to the experience of Dale (1962). In July 1973 we were forced to improvise the technique of end-to-side anastomosis joining the end of a dacron prosthesis to the side of the vein graft for a femorodistal popliteal bypass. During the ensuing 15 months we have carried out this composite graft only when the greater saphenous vein was not of adequate size throughout. In 17 limbs the composite graft was placed between the common femoral artery and the distal popliteal artery and on 6 occasions to the posterior tibial and peroneal arteries. Nineteen limbs exhibited either gangrene, impending gangrene, ischemic ulceration or severe rest pain. In four extremities intermittent claudication of a progressive and disabling degree was the indication for operation. Eleven of the 22 patients were diabetic. Run-off beyond the popliteal artery was poor in 16 of the 23 limbs and inflow was subnormal in three patients. During the followup period, 10 grafts have occluded, one day to 6½ months postoperatively, two due to inflow deficiency, 5 due to poor outflow, one to an error in technique, and two occluded without known cause. Two patients came to major amputation following closure of their grafts, 3 and 7 months postoperatively. Results with the composite graft are compared with the bovine heterograft and the homologous vein graft.

ON JULY 18, 1973 during an operation on a 66-year-old diabetic woman a serious problem arose which led the authors to improvise a technique for the construction of a composite dacron vein graft bypass to the distal popliteal artery. We had joined a reversed

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saphenous vein to an isolated segment of the distal popliteal artery and to the proximal superficial femoral artery. Unfortunately the vein was of good size (6 mm) for only 15 cm then was only 3 mm in external diameter for the portion used proximally. Under observation pulsation ceased in the graft within a few minutes. Our experience with dacron prostheses to the distal popliteal artery in patients with angiographically poor run-off had been dismal and as no homologous vein graft was available, we then joined one end of a 6 mm knitted dacron prosthesis to the proximal superficial femoral artery and the distal end of the prosthesis end-to-side to the larger half of the saphenous vein (Fig. 1). The patient's paratally gangrenous toe demarcated and healed following the procedure although no pulsations were ever noted in the foot. She remained well until 7 months postoperatively, when the graft occluded and an above-knee amputation was required.

From July 18, 1973 until September 30, 1974 we have employed this technique in 6 patients for bypasses to the tibial and peroneal arteries, 17 limbs in 16 patients to the distal popliteal artery and in 8 patients to the proximal and middle thirds of the popliteal artery.

Our own experience with fluted end-to-end dacron vein composite grafts was poor due to early thrombosis in days or weeks in several patients operated upon during the 1960s and was similar to the experience of Dale, Pridgen and Shoulders¹ reported in 1962. Of their 16 grafts, closure was noted in 13 by the seventh postoperative month.

In November 1973 we first learned of Linton and Wirthlin's⁴ experience with composite dacron autogen-

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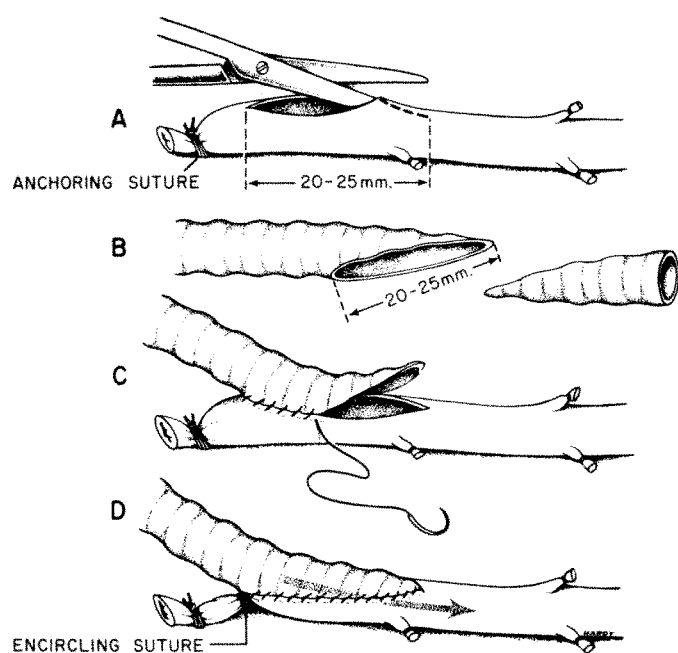


FIG. 1. Authors' technique of end-to-side anastomosis of prosthesis to vein graft.

ous vein bypass grafts to the distal popliteal artery. They employed a long end-to-end streamlined anastomosis between a 6 mm knitted dacron prosthesis and the saphenous vein in 40 patients followed from one month to more than 6 years. At 6 months 80 per cent were patent and 60 per cent were patent at 2 years (Fig. 2). By comparison their experience with autogenous vein grafts shows a patency rate of 90 per cent at 6 months and 80 per cent at 2 years.

Our technique of joining the dacron prosthesis in an end-to-side manner to the saphenous vein may appear

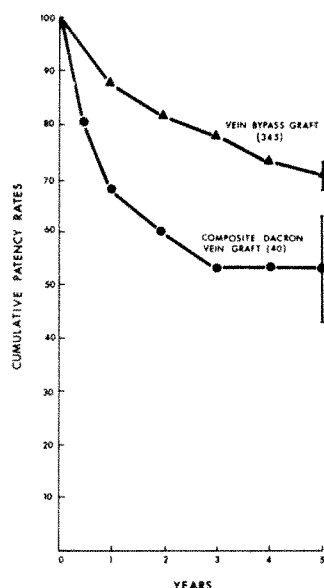


FIG. 2. A graph showing cumulative patency rates for 40 composite vein grafts by the life table method compared to autogenous saphenous vein bypass graft. (From Linton & Wirthlin's report⁴ on composite grafts).

FIG. 3. Patient A.G.: Postoperative angiogram showing prosthetic vein anastomosis (double arrows) and anastomosis of vein graft to mid-popliteal artery (single arrow).



quite similar to Linton's method. However there are several differences which may be of some importance. The vein is reversed and the large proximal end is joined to the distal artery in an end-to-side fashion. The vein is tunneled through the popliteal space and the proximal end is tacked down to the adductor fascia under ideal tension with the knee joint extended. An opening in the side of the vein approximately 20-25 mm is made and the 6 mm knitted dacron prosthesis is bevelled about 25 mm. With #5-0 Mersilene® a continuous over-and-over suture is placed to approximate carefully the two structures. Great care must be exercised to avoid tension on the vein by stretching the dacron. One of our failures we believe was due to the dacron pulling away from the distal end of the anastomosis one month postoperatively. To avoid this we open the vein for only 20 mm and if the opening in the dacron is longer than the opening in the vein, short increments in the venous orifice are made to afford a perfect end-to-side anastomosis. When the suture line is complete the needle is passed through and around the vein immediately proximal to the anastomosis to obliterate dead space. We believe that the advantages of this technique are: 1) The anastomosis is anchored to the deep fascia, thereby avoiding angulation, rotation, kinking, etc. 2) The vein occupies the flexor region behind the knee joint. 3) An end-to-side anastomosis is easier to



FIG. 4. Patient S.P.: Postoperative angiogram illustrating the distal anastomosis of vein to isolated segment of popliteal artery and arrow points to the only outflow vessel, viz., a lateral geniculate artery.

sites of superficial thrombophlebitis or are markedly varicose, then we have used the cephalic vein in several patients to construct a composite graft.

Case Reports

S.P., a 66-year-old diabetic man, was admitted to the hospital on March 9, 1974 with an infected deep ulcer over the head of the right first metatarsal bone of one year's duration. An angiogram showed 50 per cent stenosis of both proximal common iliac arteries, occlusion of both superficial femoral arteries and an isolated popliteal segment on the right side. An electrocardiogram revealed an old myocardial infarction. On March 12, a composite dacron vein graft was placed between the distal popliteal artery and the common femoral artery. Postoperatively a popliteal pulse (vein graft) was noted but no pedal pulses. The right foot improved temporarily and a repeat angiogram on March 26th showed the sole run-off from the popliteal segment to be a lateral geniculate artery (Fig. 4). Subsequently the right foot began to deteriorate with patchy areas of gangrene involving the heel and toes. On April 4th, a second bypass with a short segment of the left greater saphenous vein was joined end-to-side to the original vein immediately proximal to the distal anastomosis and the vein bypass was joined distally end-to-side to the mid-peroneal artery. A dorsalis pedis pulse became palpable as a result of collaterals between the peroneal and anterior tibial arteries above

construct. 4) By joining the end of the prosthesis to the side of the vein, the slightly rigid prosthesis helps to keep open the anastomosis (Fig. 1). 5) The flow is streamlined as the postoperative angiograms demonstrate, in fact in some patients the site of the anastomosis is not identifiable on the angiograms (Fig. 3). 6) The proximal anastomosis of the prosthesis is to the larger, sometimes sclerotic common femoral artery is superior to an anastomosis between a small (3-4 mm) vein graft and the sclerotic artery. This is in contrast to the diagram on page 459 of Linton's⁵ Atlas of Vascular Surgery where the illustration shows the end of the vein anastomosed to the side of a dacron prosthesis.

Indications for the Composite Graft

We believe, as do the great majority of vascular surgeons, that the autogenous saphenous vein is the best graft for the construction of femoro-popliteal and tibial bypasses at all levels but especially when the knee joint must be traversed. In certain patients, approximately 25 per cent of ours, we have found a good sized (5-7 mm) saphenous vein for 10 to 20 cm whereupon it divides into several branches none of which is over 2 or 3 mm in diameter when distended with heparinized saline solution. Under these circumstances the composite graft is most useful. When the greater saphenous veins have been stripped at a previous operation or have been the



FIG. 5. Patient S.P.: Postoperative angiogram following second procedure with jump vein graft from original vein bypass to the peroneal artery in middle third of leg.

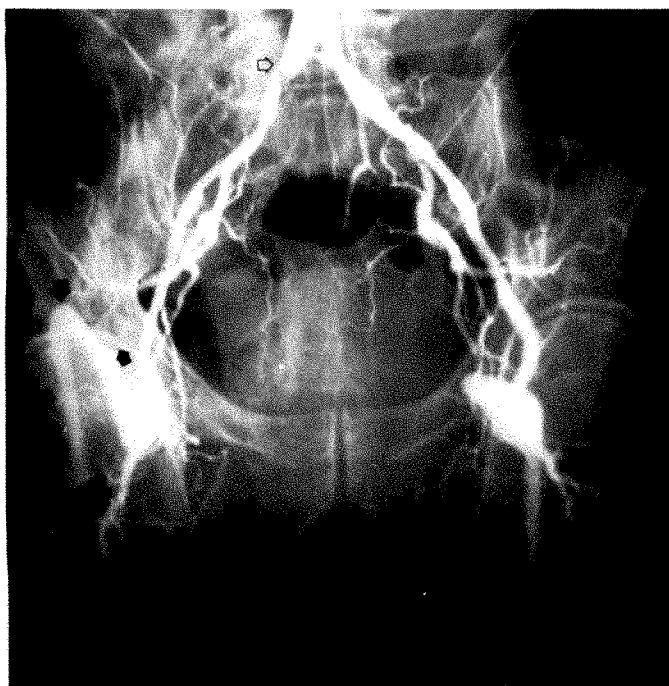


FIG. 6. Patient A.G.: Postoperative angiogram showing right common iliac arterial stenosis (open arrow) and the retrograde filling of a segment of original axillo-femoral dacron bypass (dark arrow) and the anastomosis of the composite dacron graft to the axillo-femoral graft (upper dark arrow).

the ankle. An angiogram made on April 16th is illustrated in Fig. 5. On June 17th the second and third toes were amputated with complete healing by July 1st. At present, 8 months following the insertion of the composite graft, he has a healthy foot, walks well and has a strong dorsal pedal pulse.

A.G., a 70-year-old man with progressively severe intermittent claudication of the right calf and buttock and constant rest pain of his right foot, was admitted to the hospital on July 28, 1974 for angiographic study and possibly a right axillofemoral bypass. In 1972, two years before we saw the patient, he had undergone an unsuccessful femoro-femoral bypass and two months later a successful left vein graft femoro-popliteal bypass. His past history was relevant in that there had been three hospitalizations for myocardial infarctions and two weeks prior to transfer to the Cabrini Health Care Center, an admission by his physician for an episode of severe congestive heart failure. The angiogram showed 90 per cent stenosis of a short segment of the right proximal common iliac artery, complete occlusion of the superficial femoral in the adductor canal and one vessel run-off from the distal popliteal artery.

On August 1, 1974 a 10 mm velour dacron prosthesis was inserted between the right axillary artery and the right common femoral artery. Initially rest pain disap-

peared but within 3 weeks it reappeared in spite of a functioning bypass. On September 19th a composite graft was joined to the axillo-femoral prosthesis 3 to 4 cm proximal to the right common femoral artery and the distal anastomosis was to the midpopliteal behind the knee joint. A weak dorsal pedal pulse was noticed and the patient could walk without claudication.

On October 8th, the patient noted the sudden onset of coldness and numbness of the right foot. The axillo-femoral bypass was no longer pulsating. An angiogram showed the 90 per cent stenosis of the right common iliac artery and patency of the composite graft (Figs. 6 and 3). The next day an endarterectomy of the proximal common iliac artery was carried out through an extraperitoneal approach and a new prosthesis joined to the side of the proximal common iliac artery and to the side of the proximal end of the composite graft. A strong dorsal pedal pulse developed and when last examined 6 weeks postoperatively he was walking well.

Comment

Our experiences with the two patients described in detail suggest that the composite graft will at times remain patent under the trying circumstances of a minimal inflow and a poor outflow.

Alternative Grafts

Let us examine the results of other types of available grafts for femoro-distal popliteal bypasses other than the autogenous vein.

Bovine Grafts

We have found only two papers describing their experience with bovine heterografts to the distal popliteal and tibialperoneal arteries. Slovin⁷ reported on 14 patients with 12 open at one month and a 50 per cent patency rate at 6 months. Haimov and Jacobson^{2,3} constructed femoro-distal popliteal bypasses in 11 patients and only one was patent at 12 months. One of us (G.R.) used bovine grafts for bypasses below the knee in 11 patients with 7 patent at one month and only 5 (45.4%) patent at 6 months (Table 1). We have inserted 20 bovine

TABLE 1. Bovine Grafts

	Interval	Number of Grafts		Interval Patency Rate (%)	Cumulative Patency Rate (%)
		at Risk	Failing		
Surgeon Slovin	1 mon	14	2	85.7	85.7
	6 mon	11	3	72.7	63.3
Rossi	1 mon	11	4	63.6	63.6
	6 mon	7	2	71.4	45.4
Jacobson	12 mon	11	10	9.1	9.1

TABLE 2. *Homologous Vein Grafts*

Surgeon	Interval Month	Number of Grafts		Interval Patency Rate (%)	Cumulative Patency Rate (%)
		at Risk	Failing		
Tice	1 mon	25	8	68	68
	12 mon	17	12	29.4	20
Rossi	1 mon	13	2	84.6	84.6
	6 mon	11	6	45.5	38.5

grafts for bypasses between the common femoral artery and the popliteal artery at various levels and in 3 instances, aneurysmal dilatation developed postoperatively between one and three years requiring their replacement with dacron prosthesis.

Homologous Vein Grafts

Reports by Tice and Zerbino⁸ and Ochsner, De Camp and Leonard⁶ are moderately favorable when fresh and preserved homologous vein grafts are used for femoro-popliteal bypasses. Tice reported on 25 patients with a 68 per cent (17 patients) patency rate at one month and of 17 patients followed for 12 months only 5 of the original 25 patients (20 percent) had patent grafts. One of us (G.R.) inserted 13 homologous veins to the distal popliteal and tibial arteries and 11 were patent at one month but only 5 or 38.5 per cent were patent at 6 months (Table 2). Four of the 5 patent grafts became aneurysmal between one and two years and had to be replaced.

Our own experiences with the composite graft joined to the distal popliteal and tibial and peroneal arteries is shown in Table 3. Of 6 bypasses to the tibial and peroneal arteries, 4 were patent at one month, but in 3 patients followed for more than 6 months only one remained patent. The inflow tract in all 6 was excellent, whereas the outflow tract was poor (isolated segment) in 4 and in two patients only one out of 3 vessels was patent.

Of 17 bypasses to the distal popliteal artery one failed at one month. Of 14 patients followed for at least 6 months, 9 were patent. The inflow tract was poor in one patient and only fair in 2 patients. The outflow tract was poor (isolated segment) in 7 patients and one vessel

TABLE 3. *Composite Dacron-Vein Graft*

Interval Month	Number of Grafts			Interval Patency Rate (%)	Cumulative Patency Rate (%)
	at Risk	Failing	Death		
1 mon	23	3	0	87	87
6 mon	15	7	0	53.3	46.4

TABLE 4.

Inflow Tract	
Good	20
Fair	2
Poor	1
Outflow Tract	
Good (2-3 vessels open)	7
Fair (1 vessel open)	5
Poor (Isolated Segment)	11

patency beyond the popliteal artery was noted in 3 other patients (Table 4).

During this same 15 month period we have joined the composite dacron vein graft distally to the middle and proximal thirds of the popliteal artery and the prosthesis proximally to the common femoral artery in 8 patients. All were patent at one month, and of 3 patients followed for 6 months all were patent. The inflow tract was good in 7 of the 8 patients whereas the outflow tract was poor (isolated popliteal segment) in 4 of the 8 patients.

Discussion

A new technique for the construction of a composite dacron vein bypass graft is described and has been used in 31 extremities between July 18, 1973 and September 30, 1974, 23 of the bypasses extending to the distal popliteal or one of the tibio-peroneal arteries. In all but 4 the indication for operative intervention has been rest pain, impending or actual gangrene of the toes. The four other patients had progressively severe intermittent claudication. We firmly believe that this type of graft should not be placed in patients with only moderate intermittent claudication.

Although our experience has only a short followup period, it tends to confirm that of Linton and Wirthlin⁴ which extended over several years. The difference in technique may be advantageous to surgeons of less experience than Linton and his associates. In comparison with the autogenous vein bypass graft there is a lower patency rate in our hands as well as in Linton's. On the other hand our data combined with Linton's, points clearly to the superiority of the composite dacron vein graft over the bovine heterograft, the homologous vein graft and the dacron grafts for bypasses extending below the knee joint. In fact our early results with bypasses of the occluded superficial femoral artery where the distal end of the composite graft is placed in the mid or proximal popliteal artery may make it the graft of choice over the pure dacron graft in this area.

Another advantage of the composite graft over the bovine heterograft and the homologous vein graft is the relatively low incidence of aneurysmal formation with autologous veins and dacron prostheses.

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DISCUSSION

DR. GEARY L. STONESIFER, JR. (Baltimore, Maryland): Dr. Lord has presented a fascinating paper in which he has dealt with some of the most difficult problems in peripheral vascular surgery. I think the kind of result he has gotten is certainly remarkably better than the natural course of the disease for this particular group of patients. This type of patient seems to undergo progressive deterioration, regardless of many measures that we undertake.

It's fortunate that this particular group of patients has such poor veins, but that is associated with ischemia.

We have taken a different approach to this group of problems, and I think we will continue to do so until we see further results from Dr. Linton and Dr. Lord. We have undertaken a radical deep femoral reconstruction. We devised the procedure some 22 months ago, and it consists of performing an endarterectomy for approximately 8–12 cm along the deep femoral artery. Then we perform an orifice endarterectomy at each of the branches of the deep femoral artery. The proximal portion of the superficial femoral artery, which is occluded in all of these cases, is then used as a flap to enlarge this channel. A very remarkable blood flow can be established by this technique.

The flow into the deep femoral system (which we believe is always patent if the limb is viable no matter how ischemic it looks) is such that we have had improvements in the resting pressure at the ankle, from levels which are virtually unobtainable to ranges of 40–110 mm Hg.

We have done approximately 28 procedures. We had two immediate failures. The rest of the procedures all went well initially. I know of two late failures. Again, this is only a 22-month cumulative experience. We are very pleased. Gangrenous areas have healed and rest pain has been relieved. Some of the 26 limbs that were reconstructed were in patients who had aortofemoral bypasses and in whom we did this procedure to supplement the aortofemoral bypass. In some of these patients we restored popliteal and even foot pulses.

We are pleased with this procedure, and will continue to use it and to evaluate it until we learn more about the composite grafts.

DR. W. ANDREW DALE (Nashville, Tennessee): When the saphenous vein is not suitable for femoro-popliteal grafting to a level below the knee, there are at least seven alternatives besides the one discussed by Dr. Stonesifer. First, the contralateral vein may be used. That involves more extensive dissection, and may be contraindicated if the other leg is also diseased.

Second, an arm vein may be used. Third, a bovine heterograft is probably not in order if the knee joint is to be crossed and anastomosis is to be made to a very small artery. Fourth, the Sparks mandril principle is probably sound, but details are not yet worked out, and it has been disappointing to us. Fifth, an homologous vein offers a possi-

bility, whose outlook is not optimistic. Sixth, a synthetic graft below the knee has a lower late patency rate.

The composite graft described by Dr. Lord is an attractive seventh alternative. Our laboratory experience, reported initially in 1960, was favorable, but 16 of 17 composite grafts in patients failed within a year; so that we published a reappraisal in 1962, and retracted the earlier communication.

Dr. Lord's composite is different from ours in only two ways. First, it is Dacron, rather than Teflon; and second, it has a long side anastomosis, rather than the fluted end-to-end anastomosis by us. Perhaps these differences will allow a better long term result. If so, the composite will be of value in a number of patients, and not just for isolated, last-ditch cases.

Dr. Robert Linton's recent similar report appears to agree with Dr. Lord's results, and I certainly hope that long-term patency will continue to be good. The importance of careful followup studies with angiography is obvious.

May I ask a final question about the size of the synthetic graft, which I don't believe you stated?

DR. JERE W. LORD, JR. (Closing discussion): Dr. Stonesifer, your point is well taken, and we have been slow in adjusting to it. We have used the profunda femoral artery by enlarging its orifice. Sometimes we do bypasses to it, but not for the exact reasons that you cited. It seems to me, if my memory is correct, that in Chicago at the vascular meetings last June, several authors emphasized this approach, and implied that it had worked well. Also some of the articles from the United Kingdom go in that direction. Profundoplasty may be the better way, because, as Dr. Stonesifer pointed out, if the foot is still viable with a blocked superficial femoral artery and an isolated segment in the popliteal artery, there must be some blood getting there. If it is possible to open further a sclerotic and stenotic profunda femoral artery for 1 cm or for 12 or 15 cm, the procedure should work well.

Dr. Dale, we use a 6 mm Dacron prosthesis. We happened to hit upon it just because it seemed to be the right size. Dr. Linton in his paper states that is the size he uses. We have used the cephalic vein on a couple of occasions where there was no saphenous vein available. In the group of eight patients where the graft was placed between the common femoral artery and the popliteal, in the mid or proximal thirds, all eight are working well.

This study has only a 15-month followup, and long-term results will have to await the passage of time. However, in the absence of a good vein graft, when we are faced with the decision to use a dacron prosthesis, a venous homograft or a bovine graft for an above-knee femoropopliteal bypass, we prefer to insert the composite vein-Dacron graft.

Pulmonary Responses of Unilateral Positive End Expiratory Pressure (PEEP) on Experimental Fat Embolism

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The role of positive end expiratory pressure (PEEP) was evaluated in preventing the deleterious mechanical respiratory effects of fatty acid pulmonary embolism. One group of animals had ventilation without PEEP, while the second group had PEEP of 10 cm H₂O applied only to the right lung. In the right lung, PEEP slightly reduced the blood flow, increased the vascular resistance, but reduced interstitial edema and reduced the degree of shunting to almost normal. Hypoxemia was prevented in the right pulmonary venous system, but was prominent in the left. The hypoxemia and shunting in the left lung were comparable to the Group I animals without PEEP to either lung. These studies confirm the value of PEEP in the therapy of the pulmonary manifestations of fat embolism which are the lethal factors in the fatty embolism syndrome.

THE EFFECTIVENESS of positive end expiratory pressure (PEEP) has been well documented in patients with acute pulmonary insufficiency from many causes. PEEP increases functional residual capacity, decreases shunting across the lung and may retard the development of pulmonary interstitial edema. Our previous study of an experimental fat embolism model showed that PEEP reduces the pressure gradient across the alveolar-capillary bed and prevents the fall in PaO₂ due to shunting.¹⁰ This present study examines the hemodynamic changes and physiologic shunting across the right and left lungs after fat embolism as influenced by unilateral PEEP, using the contralateral lung as well as the lungs in animals with no PEEP as controls.

Methods

Twenty-three adult mongrel dogs were anesthetized with pentobarbital, intubated with an endotracheal tube and ventilated with room air. Catheters were inserted into a femoral artery and femoral vein. After thoracotomy through the left fifth interspace, catheters were inserted in the pulmonary artery (PA), left atrium,

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right atrium, and the right and left lung pulmonary veins (PV) for monitoring pressure and blood gases. Electromagnetic flow probes were placed around the main and left PA to measure total cardiac output and differential flow to the right and left lungs (Fig. 1). Following catheterization, the endotracheal tube was changed to the tracheal divider (Kottmeir endobronchial catheter) which was passed through a tracheostomy. The separate endobronchial tubes were connected to two Harvard volume respirators which were fixed at the same cycle and tidal volume of 9 cc/kg per lung at a rate of about 10 per minute to maintain a normal pCO₂. The animals were repositioned in the supine position and the chest wall reapproximated. After steady state was reached, oleic acid at 0.075 ml/kg was administered via the right atrial catheter.

The animals were divided into two groups. In Group I (11 dogs) both lungs were ventilated with room air for two hours; then changed to 100 per cent oxygen for 20 minutes to allow calculation of the physiologic shunting and then continued on ventilation with room air for 30 minutes (Fig. 2). In Group II (12 dogs), both lungs were ventilated as Group I for one hour after injection of the oleic acid; then the right lung was ventilated with PEEP of 10 cc of water while the left lung received no PEEP. After the second hour, 100-per cent oxygen was given for 20 minutes as in Group I to calculate the physiologic shunting. For this determination, blood was drawn separately from the right and left lung pulmonary veins. The PEEP was then continued with room air for another 20 minutes after which PEEP was discontinued from the

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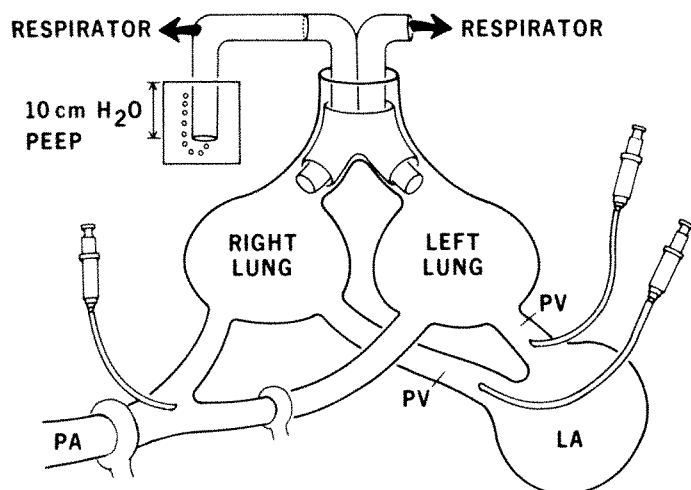


FIG. 1. Diagram of experiment showing unilateral PEEP on right with flow probes showing total and differential lung flows and differential sampling catheters in pulmonary veins.

right lung and further observations made 10 minutes later.

Results

All of the animals receiving the oleic acid survived the period of observation though none of the animals were ultimate survivors. Those dying early usually developed progressive hypotension and hypoxia and died a respiratory death or developed ventricular fibrillation.

Hemodynamic Changes

Following injection of the fatty acid, all animals in both groups showed a progressive systemic hypotension with a fall of over 20 mm Hg mean throughout the first two hours of the experiment (Fig. 3). By the end of the experiment, the Group II animals had returned to control systemic pressures whereas Group I animals' pressure had fallen by an average of 25 per cent, ($P < 0.001$). Cardiac output (Fig. 4) was maintained during the first hour but then progressively fell during the remainder of the exper-

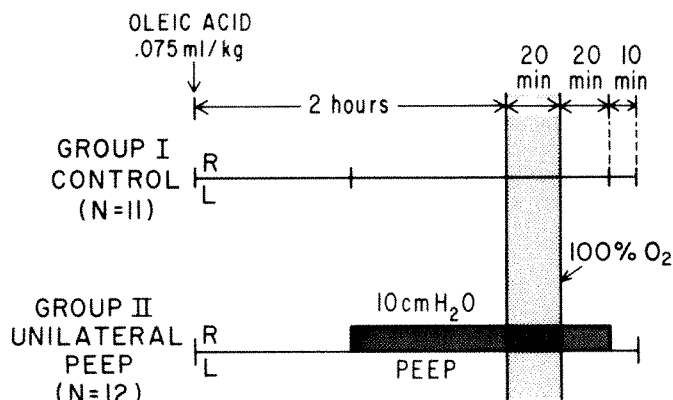


FIG. 2. Experimental Design—PEEP was started 1 hour after the oleic acid was injected. 100% O_2 was given for 20 minutes to calculate shunting.

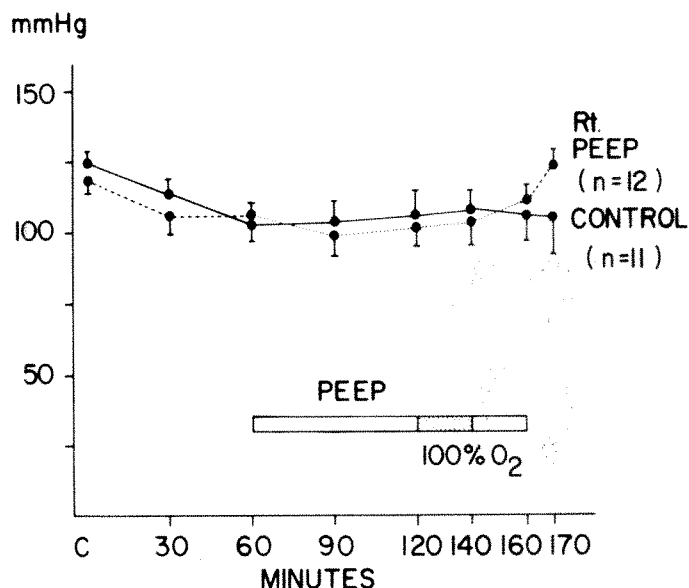


FIG. 3. Graph of mean systemic pressures in Group I (control) and Group II (right PEEP). Average values $\pm$ 2 S.E.

iment. At 90 minutes, Group I averaged 66.4 ml/kg compared to 59 in Group II. This was the only point at which there was a statistically significant difference.

The central venous pressure rose slightly but not significantly in both groups; the left atrial pressures showed a slight fall in Group I but was maintained at the control level in Group II. The greatest difference occurred at the end of the experiment but even then there was only a difference of 1.3 mm Hg between Group I and Group II (Fig. 5).

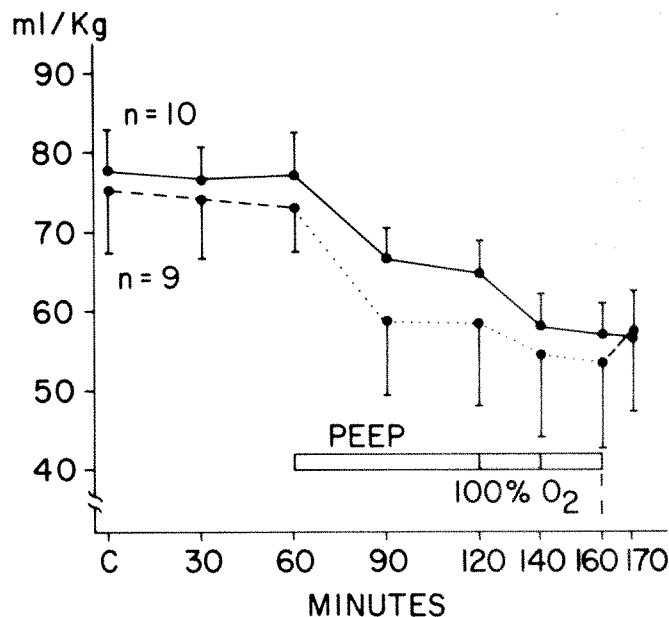


FIG. 4. Graph of mean cardiac outputs for Group I (solid line) and Group II (dashed line).

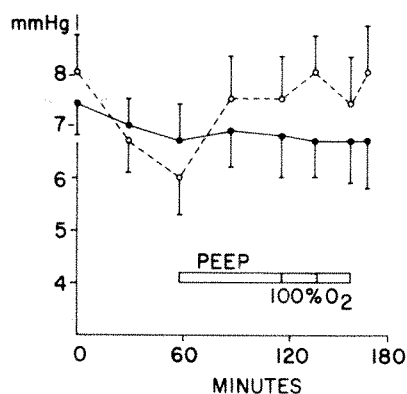


FIG. 5. Mean left atrial pressures.

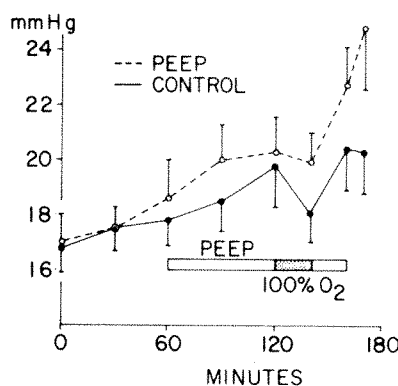


FIG. 7. Mean pulmonary artery pressures in Group I and Group II.

The right pulmonary flow (Fig. 6) represented approximately 65 per cent of cardiac output in Group I and fell to a low of about 60 per cent at the end of the experiment. In Group II, the flow through the right lung fell from 60 per cent at the onset to 50.8 per cent at the end of PEEP ($P < 0.01$). Ten minutes later the right lung flow had risen to 57 per cent of the total cardiac output.

Pulmonary artery pressure in both groups showed a slow progressive rise (Fig. 7) which was greater in the Group II animals with PEEP, especially at the end of the experiment ($P < 0.05$). Pulmonary vascular resistance in the right lung was significantly higher throughout the period of PEEP (Fig. 8).

Blood Gases

The pH fell significantly in both groups to about 7.25 with no significant difference between the two groups. PCO_2 was maintained between 35 and 40 in both groups. The arterial PO_2 fell in Group I from a control of 68.1 mm Hg to 37.8 or 55 per cent of control at the end of two hours. In Group II, it fell only to 48 mm Hg but rose to 124 after 100 per cent oxygen compared to 101 mm Hg in Group I ($P < 0.01$).

Initially, the mixed pulmonary venous blood was slightly less saturated in Group II than in Group I. After addition of PEEP, the PO_2 of the right lung pulmonary venous blood rose significantly and this difference was even more marked after 100 per cent oxygen breathing (Table 1). The total pulmonary shunt was markedly reduced by unilateral PEEP (Fig. 9) but the effect was due solely to the reduced shunting in the right lung. Shunting in the left lung remained essentially the same as in Group I controls.

Pathologic Findings

Grossly the lungs appeared markedly congested with patchy hemorrhagic consolidation. The main bronchi contained large amounts of edematous fluid which likewise drained from the raw surfaces on cut section. Grossly the right lung with PEEP had less edema and appeared less involved.

Microscopic examination of the lung sections revealed pulmonary congestion, edema fluid in the alveolar spaces and perivascular interstitium, and focal hemorrhages as common features in both the untreated and PEEP lungs. However, the untreated lungs had a more intense alveolar capillary congestion and widening of the alveolar walls secondary to accumulation of fluid in the alveolar interstitium. There were also many instances of hyaline membranes incorporating cellular debris and a more densely eosinophilic alveolar exudate suggestive of high protein content. The PEEP lung sections did not show

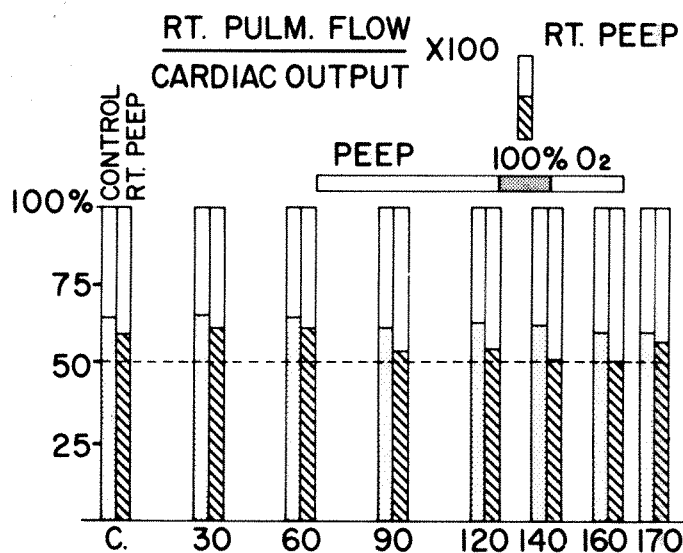


FIG. 6. Graph depicting mean right pulmonary artery flow in Group I and Group II animals.

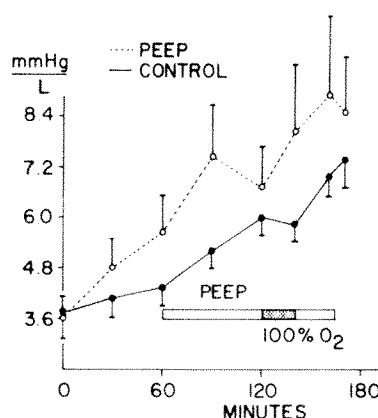


FIG. 8. Mean pulmonary vascular resistances.

alveolar wall widening or hyaline membranes, and the edema fluid appeared to contain less protein, resembling more the relatively protein free fluid that accumulates in congestive heart failure. Cellular exudate was not a prominent feature though margination of white cells in the alveolar venules was a common finding. Comparison of the findings in these lungs suggests that the composition and degree of fluid exudation was less severe in the lungs treated with PEEP.

Discussion

The pathogenesis of the fat embolism has been incompletely understood and only recently has experimental evidence been available which appears to more clearly elucidate this process. Early investigators attempted to explain fat embolism following trauma as a straight forward obstructive phenomenon caused by neutral fat globules occluding the pulmonary capillaries with resultant hypoxia. Peltier¹² clearly demonstrated that not only was this a very large amount of neutral fat required to cause death in experimental animals, but that death from neutral fat is due to pulmonary blood flow obstruction resulting in pale, anemic lungs and right heart failure. This does not resemble the clinical fat embolism syndrome as it occurs in man.¹⁵ Pathologic pulmonary findings in human fat embolism show marked inflammatory changes in the capillary bed as well as intra-alveolar and interstitial edema. These findings are markedly similar to those following an injection of a small amount of fatty acid in experimental animals. In experimental animals, it takes 30 times more neutral fat than fatty acid to cause the same morbidity.^{3,14} Most investigators currently believe that small fat globules initially lodge in the pulmonary capillaries only to be hydrolyzed into chemically active fatty acids which cause the hemorrhagic inflammatory changes in the lung.

Though definite confirmatory evidence of this theory has been elusive, there is a great deal of indirect evidence. Numerous studies show serum elevation of free fatty acids following trauma^{4,7} laboratory animals reveal an increase in pulmonary¹ and blood¹³ lipase following a neutral fat embolus; and blood lipase levels are elevated in a significant number of patients following severe fat embolism.⁷ Another potential source of fatty acids following trauma is mobilization from the fat stores of the body. It has been shown experimentally that following trauma, increased circulating catecholamines mobilize free fatty acids from the fat stores by increasing the circulating activated lipase.⁵ These circulating free fatty acids enter the lung where they may have a direct effect.

Lipolysis studies have shown that injection of neutral fat in dogs causes a persistent elevation in serum lipase levels over a several hour period and that the source of the increased serum lipase is largely the lung. Neutral fat disappears from the lung over a period of several days and while some is phagocytized, the major portion is

TABLE 1. Table of pO_2 Values in Combined Pulmonary Venous Blood of Group I and Differential Right and Left Lung Venous Blood of Group II

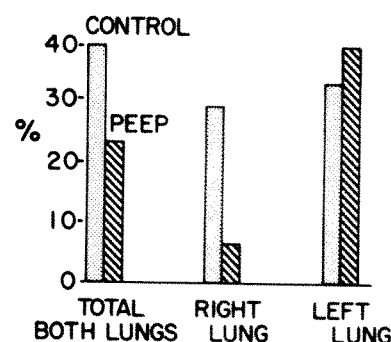
	Group I Combined	Group II Left Lung	Group II Right Lung	(PEEP)
Baseline	68.1 $\pm$ 13.6	57.2 $\pm$ 4.0	56.4 $\pm$ 8.1	NS
Room Air 2 hrs	37.8 $\pm$ 4.1	41.6 $\pm$ 3.9	76.1 $\pm$ 8.0	P<0.001
100% O ₂	101.6 $\pm$ 32.8	110.1 $\pm$ 43.6	444.8 $\pm$ 62.5	P<0.001
Mean $\pm$ 2 SE				

degraded by the lipolytic action of pulmonary lipase. Alveolar pneumocytes elaborate a lipase which hydrolyzes the neutral fat into glycerol and free fatty acids.¹¹

Ashbaugh,² using a similar dose of commercially available oleic acid in dogs, found that arterial blood pressure, heart rate, arterial oxygen saturation and cardiac index initially decreased and the PA pressure rose in all of these animals. He described severe atelectasis in these animals and felt that this contributed to the rising PA pressure. In a previous study using Ashbaugh's canine fatty acid model, we were able to demonstrate an increasing gradient between pulmonary artery wedge pressure and left atrial pressure following a fatty acid embolus.⁹ This was felt to be secondary to inflammatory obstructive changes at the pulmonary capillary bed level. Marked inflammatory changes were demonstrated in this area at postmortem. Cinemicro-photographic studies were also performed which revealed marked edema and slowing of pulmonary capillary blood flow in the pulmonary capillary bed in a similar model. Similar experiments¹⁰ using positive end expiratory pressure showed not only marked improvement in arterial oxygen tension but also a reduction in the pulmonary artery wedge to left atrium gradient. This latter suggests a reduction in the degree of interstitial edema. The use of large doses of methylprednisolone similarly has shown promise in the treatment of this entity.^{6,10}

Our current study was designed to compare hemodynamic changes and intrapulmonary shunting in one lung treated with positive end expiratory pressure with the contralateral lung without PEEP in the same

FIG. 9. Calculated Shunting—Solid bars represent Group I and cross hatch bars Group II. First set of values calculated from systemic arterial saturations, while right and left lung shunting was calculated from pulmonary vein blood. Some discrepancy due to slightly different times of sampling.



animal. As further controls, the Group I animals had the same protocol but no PEEP to either lung. Thus the right lung with PEEP could also be compared to a right lung handled similarly but without PEEP. Since PEEP was added an hour after injection of the oleic acid, this does not represent pre-treatment, but post-insult therapy and thus is comparable to a clinical situation. It is our conclusion that treatment with PEEP reduces the interstitial edema and the hemodynamic capillary block, and reduces intrapulmonic shunting. All these combine to maintain a higher systemic arterial saturation. It appeared significant that unilateral PEEP in our studies only minimally depressed cardiac output and at only one period did it significantly reduce pulmonary blood flow throughout the right lung. It did increase the pressure in the pulmonary artery as well as the right lung arterial resistance.

In the control Group I animals, shunting reached a level of 39 per cent and was essentially the same in the left lung of Group II. Shunting in the right lung with PEEP, however, was reduced to essentially a normal level of 6.69 per cent. Thus, our experiments have shown that the chemical irritant effects of free fatty acids are significant but that the pulmonary alveolar capillary function can be restored by the use of PEEP. PEEP can not only significantly decrease the amount of shunting but also can aid in maintaining normal respiratory mechanics and normal systemic oxygen saturations.

Even though fat emboli may be dispersed to many organs, the morbidity and mortality of clinical fat embolism come primarily from its pulmonary manifestations.¹¹ Clinically patients show a gradual deterioration of pH and PaO₂. The hypoxemia is due to severe perfusion ventilation abnormalities and possible defusion defects at the alveolar capillary level and the metabolic acidosis is secondary to sustain hypoxemia and hypotension. Our recent therapy has been directed toward the

control of these pulmonary changes. Positive end expiratory pressures with the use of only minimal increases in oxygen saturation has done much to decrease the morbidity and mortality of this entity and in fact, during the past three years in 13 cases, there has not been a single mortality from fat embolization at our institution.⁸

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DISCUSSION

DR. GILBERT S. CAMPBELL (Little Rock, Arkansas): The first time I'm aware that PEEP was used extensively in clinical patients was in the late 1940s in a polio epidemic in Minnesota. William Kubicek and Frederic Kottke used PEEP in the ventilatory support of patients with bulbar poliomyelitis.

PEEP has been utilized and studied by Ashbaugh, Petty, and associates of Denver and by Powers of Albany. I think it would be of advantage to all of us if Dr. Webb would give us his appraisal on the pathophysiology of how PEEP improves respiratory distress, not only in fat embolism, but in other causes of respiratory insufficiency.

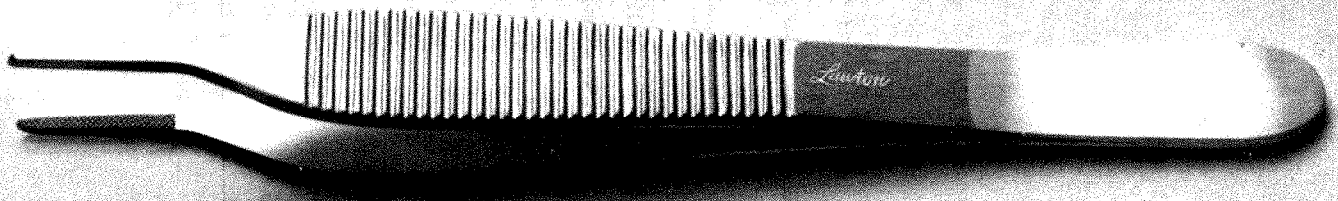
DR. WATTS R. WEBB (Closing discussion): Actually PEEP is even older. It goes back to World War II when the cardiologists were using it for the treatment of pulmonary edema from heart failure, and a paper I presented at the American Thoracic Association some 20 years ago dealt with positive and expiratory pressure, although we didn't call it by that particular name at that point; but it was for the treatment of pulmonary edema secondary to cardiac difficulties in thoracic surgery.

The reasons it works are severalfold, and the most important is probably that it opens up a large number of the alveoli. The functional residual capacity, that portion of the air that should remain in the lung at the end of expiration, is often reduced in response to inflammatory situations and in response to many other problems that we call the adult respiratory distress syndrome, fat embolism, clot embolism in particular, and various other things.

The alveoli need to be opened up, and if they can be opened, then, obviously, the blood flowing past the now ventilated alveoli tremendously reduces the shunt.

I think these pathologic slides we have shown you are the first, to me, completely convincing—and to our pathologist they are completely convincing—evidence that PEEP really does reduce the interstitial edema. There's no doubt, as we have known for a long time, that it got rid of some of the alveolar edema, which you could also suck out or cough out; but this study seems to me to prove very definitely that there is reduced interstitial edema. Also there is a marked gradient from the arterial side to the venous side across the alveolar capillaries of 4-5 mm, which for this system is large. In response to PEEP this gradient is totally removed, and flow is restored toward normal. Thus you improve both flow and ventilation.

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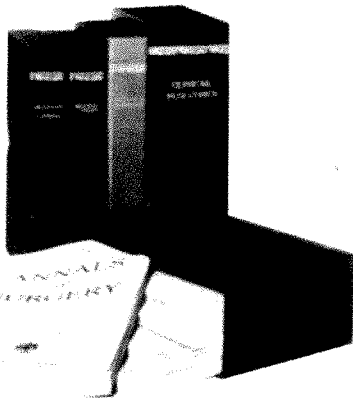


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Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

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PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

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Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

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Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdose or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

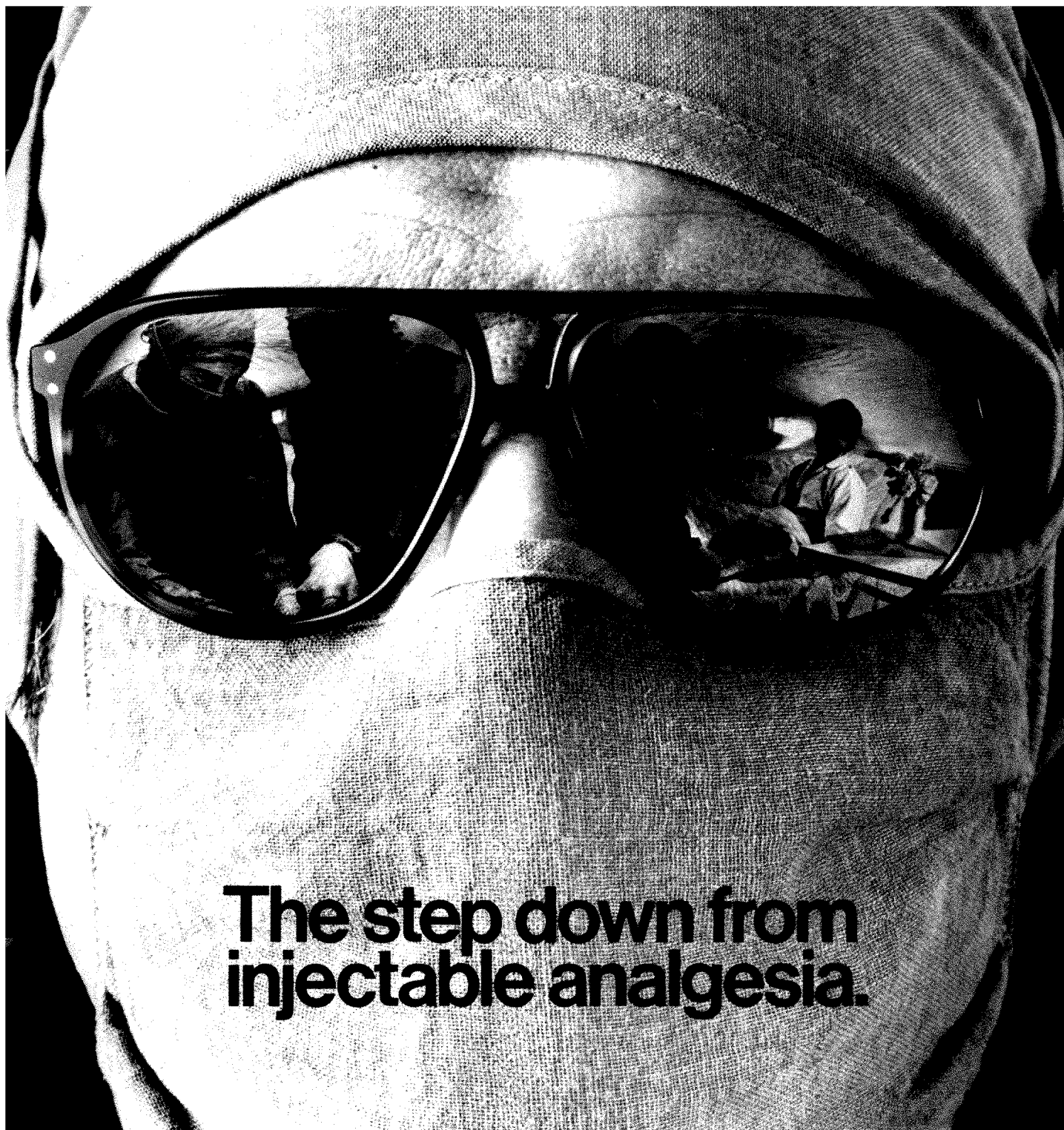
An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

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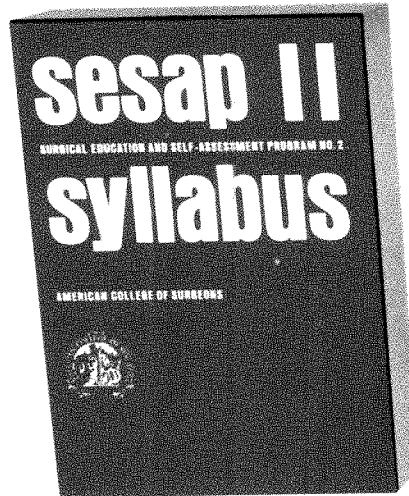
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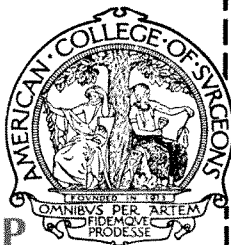
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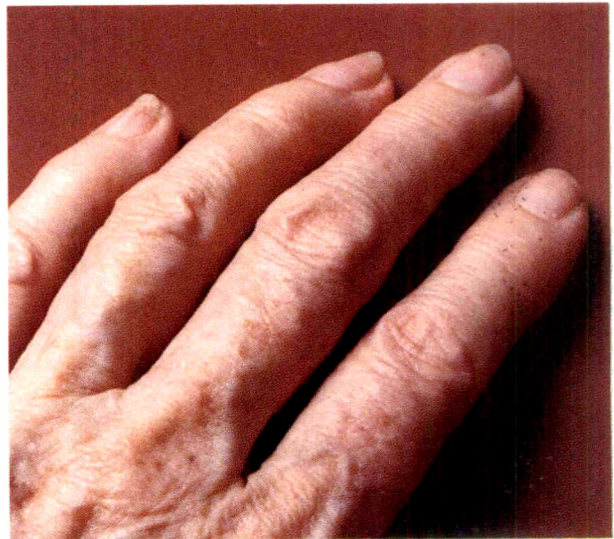
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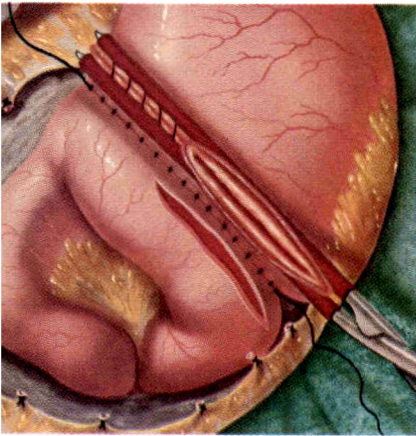
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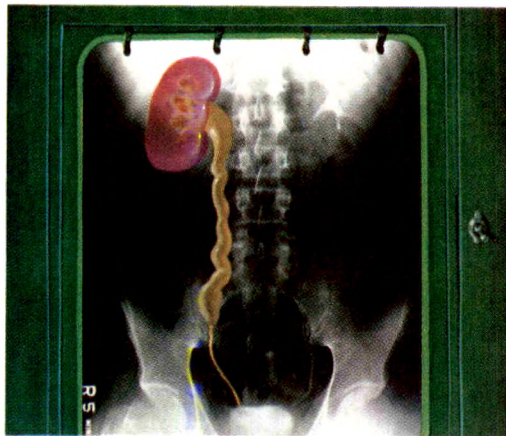
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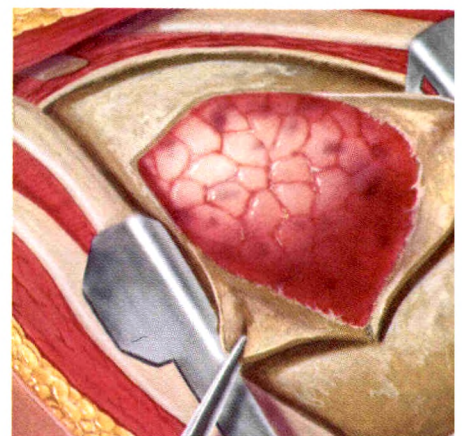
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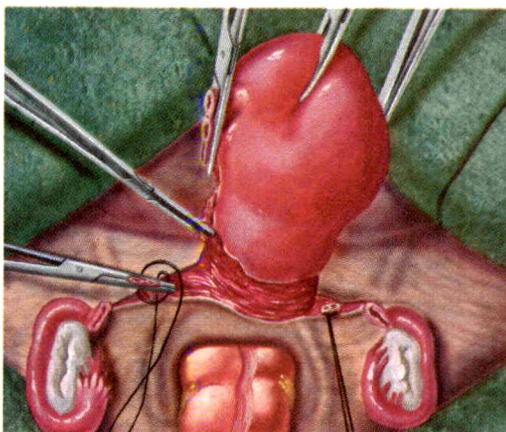
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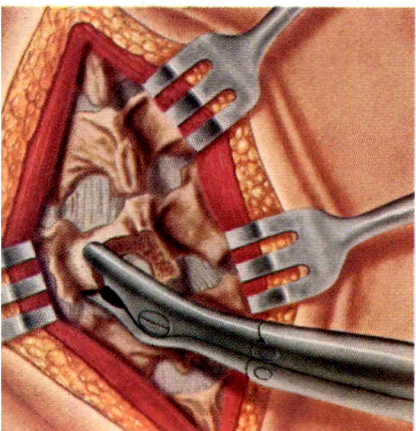
Traumatic pain



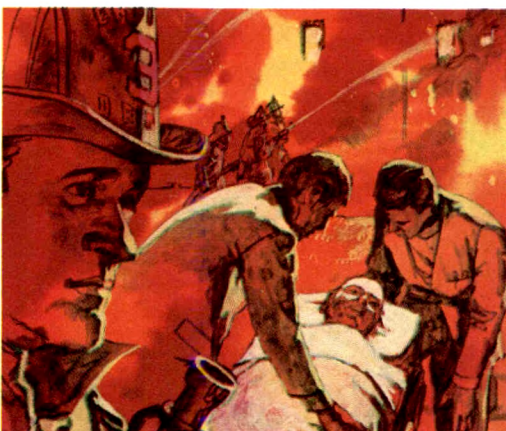
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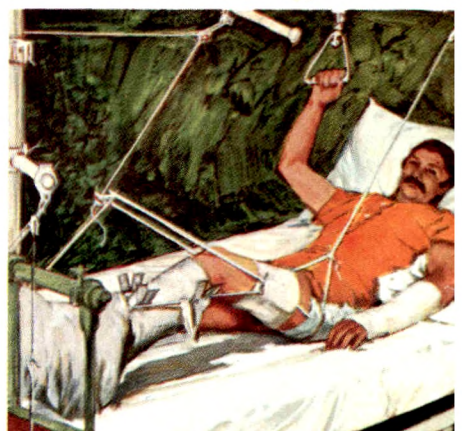
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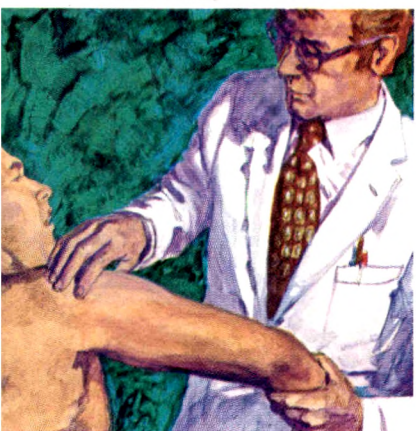
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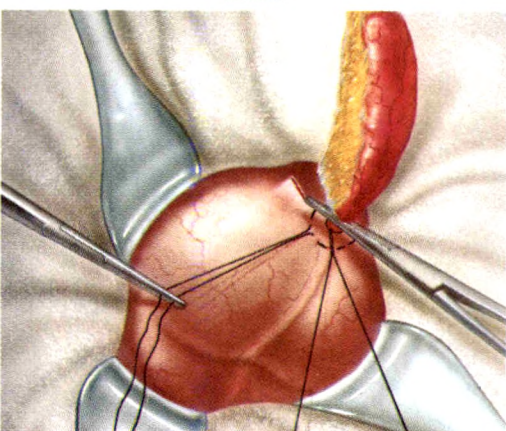
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45 mg. for I.M. or S.C. use

60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration. Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared

spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: Certain Respiratory Conditions. The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis. **Impaired Renal or Hepatic Function.** Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting. **Biliary Surgery.** Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—**respiratory:** respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; **cardiovascular:** circulatory depression, shock, hypertension; **CNS effects:** sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; **gastrointestinal:** constipation, dry mouth; **dermatologic including local:** diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; **other:** urinary retention, headache, paresis, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—**neuromuscular and psychiatric:** muscle tremor, insomnia, disorientation, hallucinations; **gastrointestinal:** taste alteration, diarrhea and cramps; **ophthalmic:** blurred vision, nystagmus, diplopia, miosis; **hematologic:** depression of white blood cells (especially granulocytes), usually reversible and

usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; **dermatologic:** soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; **other:** tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS**.

Dosage and Administration: Adults, Excluding Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: Manifestations. Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are not effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: Uni-Amp™—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.) in boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10, 25, and 100.

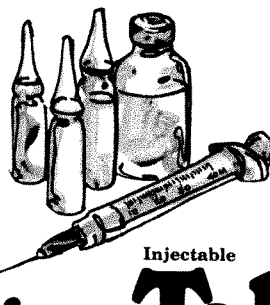
Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection. **Multiple dose vials of 10 ml.,** each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

(1639M)



**the unextreme
injectable
for serious pain**

Injectable

Talwin®
brand of
pentazocine



The Fenwal[®] Microaggragate Blood Filter

For routine use in transfusion
of stored blood

Removes microaggregates
greater than 20 microns
in size

Allows pressure infusion
at flow rates up to
100 ml per minute

Multiple units may be
infused without
significant decrease in
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Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Tigan is indicated for the control of nausea and vomiting.

CONTRAINDICATIONS: The injectable form of Tigan in children, the suppositories in premature or newborn infants, and use in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.

WARNINGS: Tigan may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. *Reye's Syndrome* has been associated with the use of Tigan and other drugs, including antiemetics, although their contribution, if any, to the cause and course of the disease hasn't been established. This syndrome is characterized by an abrupt onset shortly following a nonspecific febrile illness, with persistent severe vomiting, lethargy, irrational behavior, progressive encephalopathy leading to coma, convulsions and death.

Usage in Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or stillborn pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.

PRECAUTIONS: During the course of acute febrile illness, encephalitis, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

HOW SUPPLIED: Ampuls, 2 ml, boxes of 10. Multiple Dose Vials, 20 ml. Thera-Ject™ (Disposable Syringes), 2 ml, boxes of 10.

Many things have changed in the operating room in 15 years...

but the Tigan effect hasn't.

(trimethobenzamide HCl)

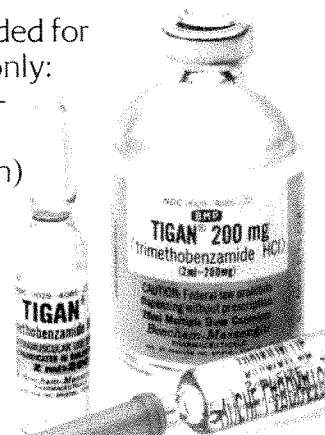


When Tigan was introduced in 1959, nausea or vomiting was a frequent post-operative occurrence. Advances in surgical technique and anesthetic agents have reduced these incidences. However, when you need control of emesis and need it quickly, Tigan provides the necessary effectiveness with a relative lack of side effects.

Tigan has been used successfully with many different anesthetics and in all types of surgery without potentiating the anesthesia, delaying the awakening or altering the patient's vital signs (although a few instances of hypotension have been reported).

Beecham

Tigan Injectable is intended for intramuscular administration only: the recommended adult dose—2 ml. (200 mg.) t.i.d. or q.i.d. (It is contraindicated in children)



For prompt control of nausea and vomiting

Tigan® Injectable

(trimethobenzamide HCl)

Collector's item

WOUND DRAINAGE IS TRAPPED INSIDE
ODOR-BARRIER, TRANSLUCENT COLLECTOR
FOR VISUAL ASSESSMENT AND
ACCURATE MEASUREMENT.



THE PROTECTOR FOR DRAINING WOUNDS

THE HOLLISTER DRAINING-WOUND
MANAGEMENT SYSTEM

KEEPS FLUIDS AWAY FROM
PATIENT'S SKIN AND GUARDS AGAINST
IRRITATION AND CONTAMINATION.

Skin-conforming Karaya Blanket protects skin around
wound site... directs discharge into Collector. There are
no messy, wet dressings to handle.

View wound site through Access Cap. Remove cap for
wound examination and drain tube adjustment. There is
no need for painful dressing removal.

Supplied sterile, for application in O.R. or patient's room.

The better alternative
to absorbent dressings.



Write for more information.

HOLLISTER

HOLLISTER, INC., 211 E. CHICAGO AVE., CHICAGO, ILL. 60611

DARVOCET-N® 100

propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions.

[011375]

DARVON® COMPOUND-65

propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

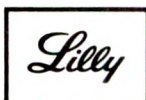
Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions.

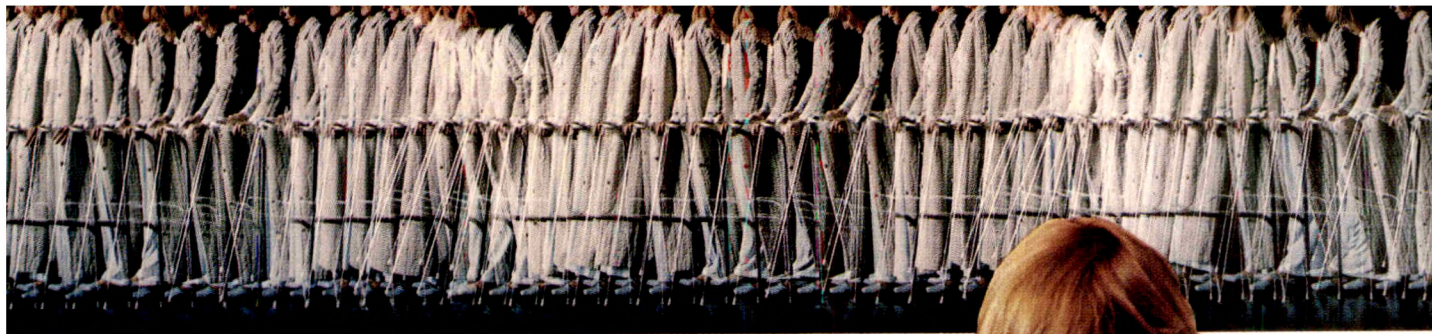
[011375]



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to the profession on request.

Eli Lilly and Company, Inc.
Indianapolis, Indiana 46206

500390



Relief from her postsurgical pain

Darvocet-N[®] 100

100 mg. propoxyphene napsylate and
650 mg. acetaminophen

contains no aspirin



Darvon[®] Compound-65

65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin



for mild to
moderate pain

See summary of prescribing information on adjoining page.





Answers to some important questions about resistance

Q: What is the nature of bacterial resistance to GARAMYCIN (gentamicin sulfate)?

A: Resistance has been shown, in the laboratory, to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported to date.

Q: What has been the experience concerning the potential for resistance to gentamicin?

A: After a year of isolating urinary tract pathogens in the laboratory of a 15-physician group practice in order to tabulate antibiotic resistance, Bauer¹ reported that common uropathogens were highly susceptible to gentamicin. Discussing their ongoing computerized studies of *in vitro* susceptibility of clinical isolates, Truant and co-workers² noted that gentamicin was the most effective *in vitro* of the chemotherapeutic agents they were

employing. In a survey of the published studies on resistance to gentamicin, Weinstein and co-workers³ found little change from 1963 to 1970 in the relatively high percentage of bacterial strains sensitive to gentamicin. *In vitro* sensitivity was determined in all cases by the tube-dilution method.

Q: Are gentamicin-resistant mutants of medical significance?

A: A laboratory study of strains resistant to gentamicin *in vitro* suggests that mutants that are gentamicin-resistant "... are probably of negligible medical significance," according to Weinstein and co-workers.³ This is because the mutants were found to need exceptionally good conditions for growth and were rather unstable genetically. Accordingly, "These characteristics result in competitive disadvantages for these strains under natural conditions..."³

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.



Q: Has there been any change over the past four years in the *in vitro* susceptibility of major gram-negative pathogens to GARAMYCIN Injectable?

A: Gram-negative pathogens, recently identified and tested, demonstrated high susceptibility (96 per cent) to GARAMYCIN. From 1970 through 1973, there was virtually no decrease in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

***In Vitro* Pathogen Susceptibility to Gentamicin, 1970-'73**

	1970	1971	1972-'73
Gram-negative Susceptibility	97%	97%	96%
No. of patient tests	9,007*	12,507*	4,642**
<i>Escherichia coli</i>	97%	98%	98%
<i>Proteus</i> species, indole-negative	98	99	97
<i>Proteus</i> species, indole-positive	98	96	96
<i>Pseudomonas aeruginosa</i>	95	95	94
<i>Klebsiella-Enterobacter-Serratia</i>	100	100	98
<i>Klebsiella pneumoniae</i>	100	100	98
<i>Klebsiella</i> , all others	97	99	98
Gram-positive Susceptibility			
No. of patient tests	2,698*	2,962*	1,122**
<i>Staphylococcus aureus</i>	96%	95%	95%

Source: I.M.S. Audit of Pathology Cultures, 1970-'73. These *in vitro* data are based on results obtained from hospitals in a nationwide audit. (*represents sample data from over 100 hospitals; **represents projections based on sample data from over 200 hospitals—add 000). The pathogens tested were obtained from all inpatient and outpatient services.

In vitro susceptibility data are not necessarily indicative of clinical effectiveness.

Q: Is R factor-determined resistance to gentamicin a clinical problem?

A: Very few problems have occurred to date with R factor-determined resistance to gentamicin. In all cases, this resistance has been controlled. In one clinical emergence in the United States, a resistant strain of *Klebsiella pneumoniae* was identified that caused an outbreak of infections at a Washington, D.C. hospital. Control measures were instituted, including a ban on the use of topical gentamicin and revision of hospital antiseptic procedures and "despite continued parenteral usage of gentamicin, the outbreak was successfully suppressed."⁴

Q: What has been the pattern of resistance to GARAMYCIN Injectable over an eight-year period (1963-1971) in investigational and clinical use?

A: One investigator noted: "In the experience so far with [gentamicin], which is 7 or 8 years, in centers where it's been restricted to parenteral use, resistance has not appreciably changed."⁵ Another authority⁶ "...found very little emergence of resistance..." during eight years of use.

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5. Jackson, G.G.: Highlights of a Symposium on Gentamicin, a filmed panel discussion summarizing a symposium on gentamicin, University of California School of Medicine, Los Angeles, January 26, 1971.
6. Cox, C.E., *ibid.*

A logical choice in serious gram-negative infections[†]

Garamycin[®]
gentamicin sulfate **Injectable**
40mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

[†] Due to susceptible organisms

See Clinical Considerations section which follows...



**In serious
gram-negative infections***

Garamycin[®]

gentamicin
sulfate

injectable
40 mg./ml.

Each ml. contains gentamicin sulfate
equivalent to 40 mg. gentamicin

- A highly appropriate spectrum for today's problem gram-negative pathogens.
- I.V./I.M. versatility.
- Little emergence of bacterial resistance to date.
- Relatively low incidence of adverse reactions when used as directed.
- Proven clinical efficacy.

GARAMYCIN[®] Injectable
brand of gentamicin sulfate,
U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate
equivalent to 40 mg. gentamicin
For Parenteral Administration

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, *Proteus* species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis),

urinary tract, respiratory tract, gastro-intestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:
*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lbs.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., 2 ml. multiple-dose vials for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., 2 ml. multiple-dose vials for parenteral administration.

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SLR-886

JANUARY 1974
AHFS Category 8:12.28

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References

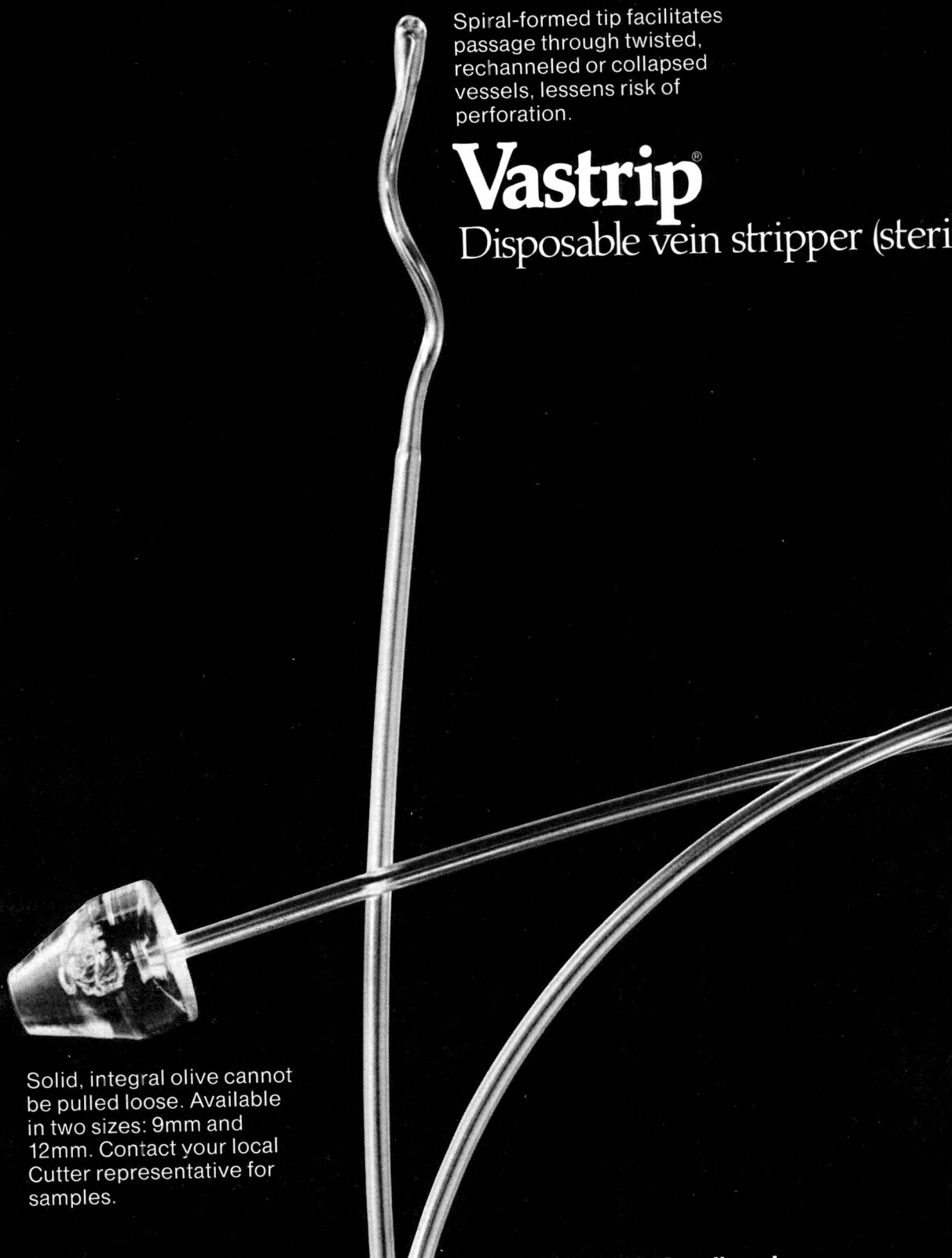
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Septic Lung and Shock Lung in Man

GEORGE H.A. CLOWES, JR., M.F., ERWIN HIRSCH, M.D., LESTER WILLIAMS, M.D.,
EDWARD KWASNIK, B.S., THOMAS F. O'DONNELL, M.D., PETER CUEVAS, M.D. V.K.
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Two series of patients were studied by serial measurements of blood gas exchange and pulmonary hemodynamics to compare the relative importance of hemorrhagic shock and sepsis as causes of pulmonary dysfunction and to evaluate the dangers of respiratory failure in post traumatic patients. There were 27 patients who had sustained profound hemorrhagic shock and massive blood replacement averaging 9.7 liters and 38 patients who suffered general peritonitis or other forms of fulminating nonthoracic sepsis. All were supported by endotracheal intubation and volume controlled ventilators. The overall mortality for the post shock patients without sepsis was 12% while in the septic patients it was 35%. The maximal pulmonary arteriovenous shunt encountered in the post hemorrhagic shock patients at 36 hours averaged $20 \pm 8\%$ and was accompanied by high cardiac indices (average $5.1 \pm 1.3 \text{ L/M}^2/\text{min}$) but no significant rise of pulmonary arterial pressure or peak inspiratory pressure (PIP). Severe pulmonary dysfunction subsequently occurred only in those patients who later became septic. The studies on the septic patients were divided according to the magnitude of the cardiac indices (the high indices averaged $4.8 \pm 1.6 \text{ L/M}^2/\text{min}$) and the low indices averaged $1.9 \pm 1.0 \text{ L/M}^2/\text{min}$. In the former, the average maximal shunt of $30 \pm 6\%$ was sustained for 4 or more days, accompanied by an elevation of PIP to $36 \pm 6 \text{ cm H}_2\text{O}$ and by Pa pressure of $28 \pm 5 \text{ mm Hg}$. The patients in low output septic shock usually had an associated bronchopneumonia and had an average venous admixture of $34 \pm 8\%$ and PIP values of $41 \pm 8 \text{ cm H}_2\text{O}$. The mean Pa pressure in this group was $29 \pm 6 \text{ mm Hg}$.

PULMONARY INSUFFICIENCY has been recognized for many years as a serious hazard of surgery and other forms of trauma. With the advent of improved means for resuscitation and for preserving the lives of seriously injured patients, it became apparent that respiratory failure was responsible for many of the subsequent deaths.^{7,9} The common association of shock in the course of such patients led to the term "shock lung" for

the syndrome of hypoxemia terminating in bronchopneumonia.^{13,17} Because loss of compliance, edema, intravascular cellular congestion, and alveolar collapse were frequently present, the terms "wet lung," "stiff lung," "congestive atelectasis" and others were applied to it. However, analysis of the courses of casualties in the Viet Nam war, by Proctor et al.,³² Bredenberget al.,⁸ Hirsch et al.²¹ and others, led to the conclusion that serious deterioration of pulmonary function seldom occurred until tissue gangrene or sepsis developed. It is significant that in an excellent recent symposium on "Pulmonary Problems in Surgery" edited by Webb³⁸ the term "Shock Lung" is not used as a title. More recently Fulton and Jones¹⁸ reviewed the admissions to their hospital for trauma and found that insufficiency developed in only 7% of the patients with hypovolemic shock only. On the other hand, sepsis was present in 91% of those who had pulmonary failure requiring respiratory support, and of all patients who became septic 42% had serious respiratory problems.

Clowes et al.^{10,14} have shown by clinical and experimental observations the sequence of events which lead to respiratory insufficiency after the onset of non-thoracic sepsis. It has become clear that in the septic course the pulmonary lesions pass through two phases. The first is accompanied by evidence of a pulmonary shunt (hypoxemia), usually in the presence of a relatively clear lung fields in the chest x-ray. The histological abnormalities include interstitial edema, leucocyte septal invasion, intravascular congestion, and diffuse alveolar col-

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TABLE 1. *Diagnoses and Mortality of Surgical Patients Studied*

Post-hemorrhagic Shock: Diagnosis	Av. Blood Replacement (Liters)	Av. Time Hypotensive (Hours)	Survivors	Subsequent Deaths	Total
Ruptured liver-trauma	11.3	3.7	9	3	12*
Ruptured ectopic pregnancy	4.8	2.1	2	0	2
Ruptured aortic aneurysm	6.4	4.2	1	1	2
Fractured pelvis (retroperitoneal hematoma)	9.1	4.2	2	1	3
Wound abdominal vessels	7.6	3.3	3	1	5
Upper gastrointestinal bleeding (peptic ulcer)	8.4	4.6	2	1	3
			19	7	27
Major Non-thoracic Sepsis: Diagnosis					
Pancreatitis-acute with peritonitis			2	2	4
Disrupted intestinal suture line-peritonitis			2	1	3
Perforated peptic ulcer			2	0	2
Duodenal necrosis			0	1	1
Gangrene or ruptured gall bladder			3	1	4
Cholangitis			2	0	2
Gangrene small bowel			2	1	3
Gangrene colon			2	2	4
Perforated colon			3	3	6
Ruptured appendicitis			3	0	3
Phlegmon pelvis			0	1	1
Retroperitoneal abscess			2	0	2
Wet gangrene leg-vascular insufficiency-amputation			3	0	3
			26	12	38

*Only 3 included in hemodynamic analysis of Table 2.

lapse.¹³ If unchecked this lesion progresses to the second phase which is the often fatal bronchopneumonia, long ago described by Moon²⁶ as the typical pulmonary lesion of shock and sepsis.

Concern for the relative importance of hypovolemic shock versus tissue gangrene and sepsis as the causative agents of pulmonary failure may appear academic. However, an understanding of the significance of each leads the clinician to institute measures for preventing the progression of the lung lesions when it is recognized which patients may be at risk.

Thus, it is the purpose of this paper to compare the data assembled on hemodynamic and respiratory functions from 27 patients after severe hemorrhagic shock with the data from 38 patients who suffered fulminating non-thoracic sepsis. In each instance injury of some form, either trauma or surgery, was combined with hemorrhagic shock or subsequent infection. The mild respiratory dysfunction induced by severe hemorrhagic shock and massive blood replacement contrasts with the severe prolonged pulmonary insufficiency which accompanies extensive sepsis. These observations are reinforced by the clinical response in 12 of the 27 post shock patients who required hepatic lobectomy for extensive liver injuries. These 12 patients constitute a relatively uniform group illustrating the early respiratory effects

compared to the severe pulmonary failure encountered in those who subsequently became seriously infected. Finally, the results of a bioassay, recently developed by our group to demonstrate the presence in the plasma of factors injurious to lung, serves further to emphasize the greater significance of sepsis in the induction of serious pulmonary dysfunction in surgical patients.

Methods and Materials

Patients were selected for study from among those admitted to the surgical wards of the Boston City Hospital during the past four years. Included are: 1) 27 patients in the post shock state due to prolonged hypovolemia from hemorrhage and 2) 38 with severe sepsis uncomplicated by hemorrhage. The nature of the injuries or illnesses and the mortality of the patients studied are given in Table 1. Only those patients are included in the post hemorrhagic shock group in whom no evidence of sepsis or major tissue necrosis was present prior to the time at which studies were initiated. All were adults; ages ranged from 19 to 73 years.

The therapeutic management of each patient was either directed by or conducted in consultation with one of the authors. In no instance was treatment altered by the studies except as indicated by data obtained in the course of their performance. Each patient was given respiratory

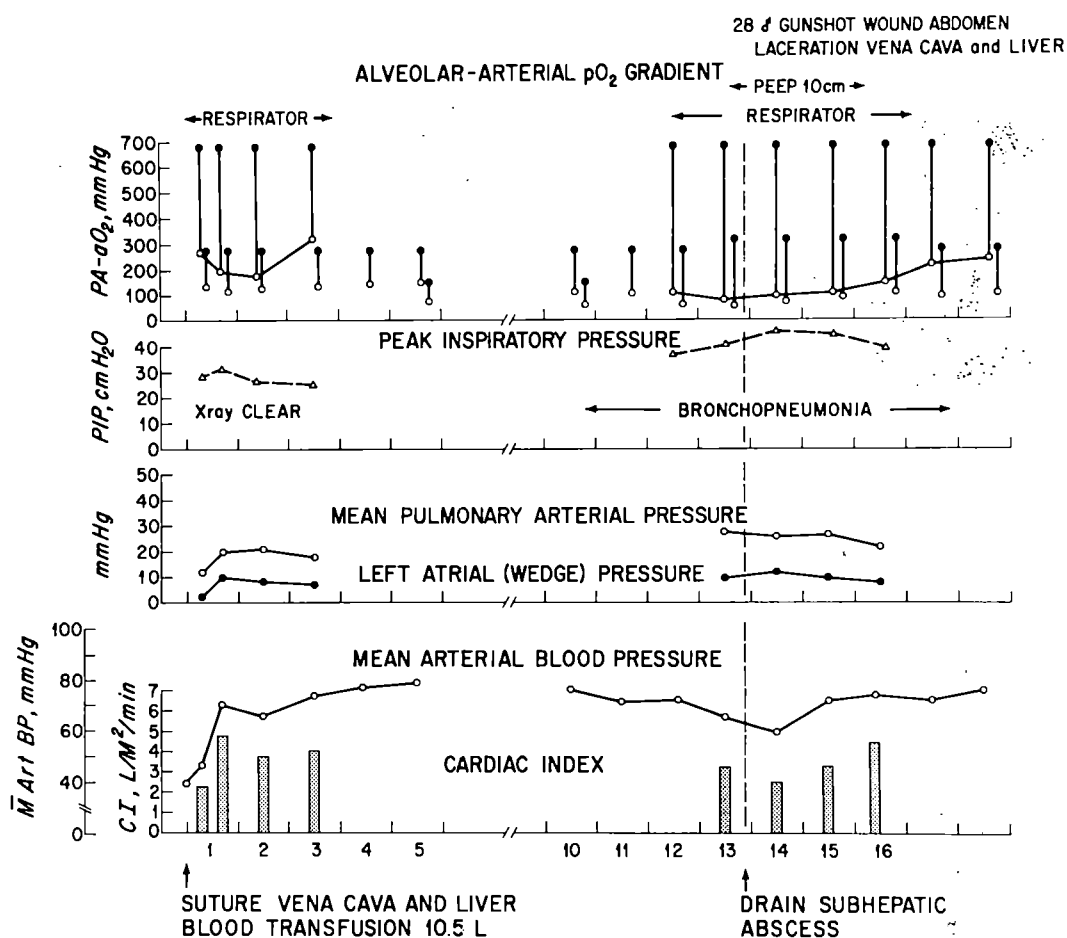


FIG. 1. Patient 1, a 28-year-old man. Note the severity of the pulmonary arteriovenous shunt, pulmonary vascular resistance, and loss of compliance after onset of sepsis with the development of bronchopneumonia which was greater than after trauma and shock.

support by a volume respiratory* at some stage of his course when indicated by the presence of hypoxemia or other evidence of pulmonary insufficiency. Ventilatory rate and tidal volume were adjusted to maintain the arterial CO_2 tension (P_{aCO_2}) at value between 30 and 40 mm Hg. Within the past two years all patients in whom severe respiratory insufficiency was anticipated were also given postoperative respiratory support by a ventilator for 24 hours or more, to be discontinued when evidence from trials of spontaneous respiration demonstrated adequate gas exchange and ability to perform the work of breathing.

Arterial blood gasses which included oxygen tension (P_{aO_2}), carbondioxide tension (P_{aCO_2}) and pH were measured with IL Blood Gas Analyzer.† Their severity of a pulmonary shunt was determined by administering a respiratory mixture containing 100% O_2 for period of 30 minutes. When mixed venous blood was available from the pulmonary artery via a Swan Ganz catheter,³⁶ a modification of the formula of Berggren⁴ was used to calculate the % of venous admixture (Shunt).⁴⁰ Otherwise, the alveolar-arterial oxygen gradient ($PA-aO_2$) was employed to estimate the % shunt using the normogram published by Pontoppidan et al.²⁹ At all other times FIO_2 was maintained below 0.5 unless severe hypoxemia necessitated

higher oxygen concentrations in the respiratory mixture. The degree of pulmonary compliance was estimated by recording the peak inspiratory pressure (PIP) from the respirator at tidal volumes and rates adequate to maintain the arterial pH and carbon dioxide tension near normal.

The hemodynamic measurements included central venous pressure (CVP) and arterial blood pressure (Art BP). Cardiac outputs (CO) were measured by indocyanine green dye dilution, and converted to cardiac index (CI) for purposes of comparing one patient with another. When indicated for measurement of circulatory dynamics, a Swan-Ganz catheter³⁶ was introduced via an antecubital vein for determination of pulmonary artery and left atrial (wedge) pressure. By means of thermal dilution the Swan-Ganz catheter also permitted measurement of CO using the "Thermocon" computerized recorder.§ Daily intravenous infusions of crystalloid fluid, colloid, and whole blood as well as urine outputs and other drainage were recorded.

*Emerson, Ohio 560, & Bennett MA-1

†Manufactured by Instrumentation Laboratories, Inc., Boston, Mass.

§Manufactured by Olson Medical Sales Company, Ashland, Mass. 01721

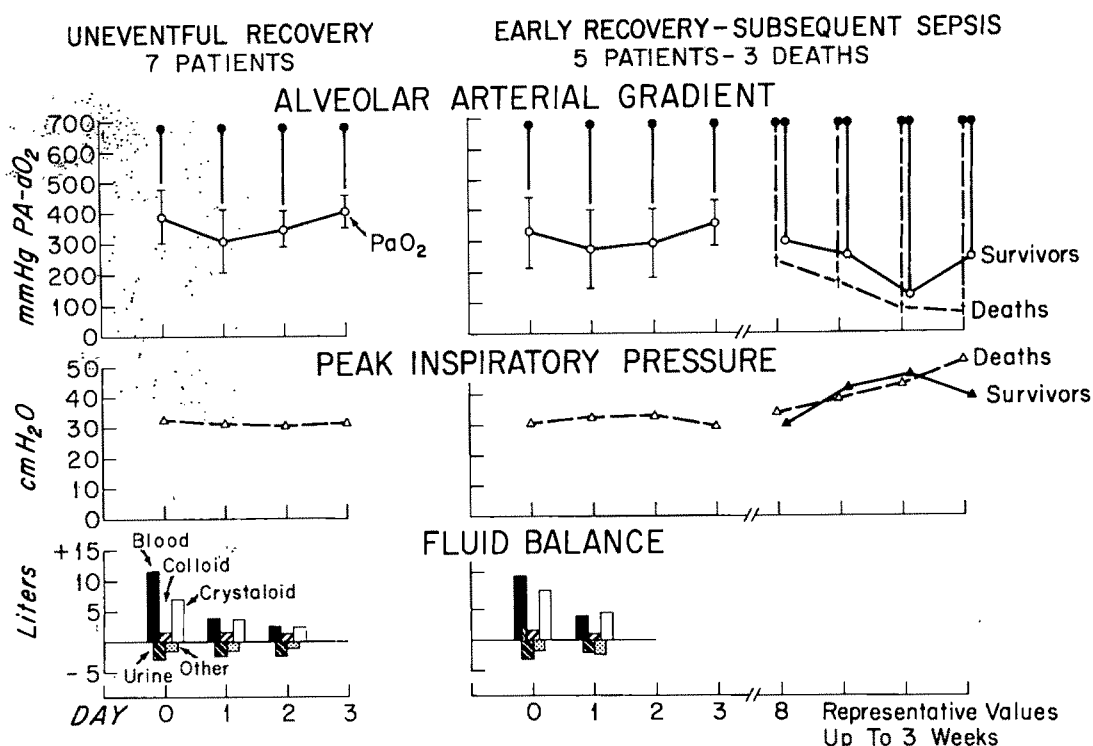


FIG. 2. The comparative courses of 12 patients who sustained severe trauma to the liver necessitating hepatic lobectomy and massive blood replacement.

The plasmas of 5 post shock patients and 12 septic patients were tested at various stages of their illnesses for the presence of endotoxin. The Limulus lysate assay was employed as described by Rheinhold et al.³³

The bioassay for circulating substances injurious to lung depends upon the development of edema and an increase pulmonary vascular resistance when 5 ml of a test solution is introduced into the perfusate of a rabbit lung. An endotracheal tube is introduced. Washed clear of all blood, the lungs are perfused in situ with a blood free mixture of gelatin (5% in Ringer lactate solution) buffered with phosphate to pH 7.2. The perfusion rate is adjusted to produce a pressure of 15 to 20 mmHg. The insufflation pressure and the perfusion pressure both are recorded. A positive reaction is recognized by an increase of 25% or more in the perfusion pressure and by an increase of peak inspiratory pressure as edema develops. The preparation does not react to as much as 0.5 mgm of endotoxin²⁰ or to the plasma from normal people when introduced into the perfusate. If, after one half hour following the injection into the perfusate of 5 ml of plasma to be tested, no reaction has occurred, the preparation is tested with 0.005 mgm of histamine to be certain that it is reactive. Should edema or pulmonary hypertension not occur in response to histamine the test is discarded. To be certain that protein in the plasma is not causing the reaction a fraction is prepared by cold pressure filtration containing only substances with molecular weights ranging from 1,000 to 10,000. Only when this "active fraction" produces a reaction in the

rabbit lung the test is considered to be positive.

Case Reports

Figure 1 illustrates the clinical course of a 28-year-old Caucasian man who received a gunshot wound. The bullet traversed and severely damaged the right lobe of the liver, passing diagonally downward through the vena cava. A portion of the right lobe of the liver was resected, the vena cava was sutured and drains were placed. During resuscitation, the surgical operation, and in the immediate postoperative period he received intravenous infusions of blood (11.5l), Ringer's lactate solution (7.0l), and colloid (1.0l). An endotracheal tube and ventilatory support were maintained for 3 days. On the seventh day rectal temperature rose to 101.6°F. Subsequently, fever increased daily. Bronchopneumonia was demonstrated on the tenth day, and respiratory support was initiated on the twelfth day. A large subhepatic abscess was drained on the thirteenth day.

Figure 2 illustrates the comparative courses of 12 patients who sustained severe trauma to the liver necessitating hepatic lobectomy and massive blood replacement (Table 3). All were treated with endotracheal intubation and ventilatory support for three days. No serious early pulmonary dysfunction occurred in any of the patients. However evidence of intraperitoneal infection became apparent from 8 to 13 days postoperatively accompanied by rapidly deteriorating pulmonary function in five patients. All were intubated and placed on ventilators. Of the five septic patients, three died. Although there was no significant early differences between the survivors and those who later became septic, note the hypoxemia and greater peak inspiratory pressures after the onset of infection.

Fig. 3 shows the clinical course of a 32-year-old American Indian male who suffered a traumatic subacute rupture of the spleen necessitating a splenectomy on the second hospital day. Three days later his rectal temperature rose dramatically to 103.6°F accompanied by a fall of mean arterial blood pressure to 52 mm Hg. Abdominal tenderness led to laparotomy at which time a traumatic pancreatitis and gas in the gall bladder were discovered. A cholecystostomy was performed. Aerobic

TABLE 2. Respiratory and Hemodynamic Maximal Responses in Uneventful Surgical Convalescence, Post-hemorrhagic Shock, and Septic States

Measurements	Uneventful Convalescence*	Post Shock ⁺	Non-thoracic Sepsis (Total 38 Patients)		
			Onset-Day 1 (12 Patients)	High Cardiac Output (30 Patients)	Low Cardiac Output (18 Patients)
<i>Respiratory</i>					
PaO ₂ (F ₁ O ₂ =0.2) (mmHg)	76±8(26)	62±8(12)	68±26(8)	57±10(15)	52±12(8)
PaO ₂ (F ₁ O ₂ =0.4) (mmHg)	—	122±38(15)	102±34(7)	73±24(28)	68±16(12)
PaO ₂ (F ₁ O ₂ =1.0) (mmHg)	388±44(6)	198±50(24)	201±45(12)	108±38(26)	106±29(16)
Shunt Estimated	12±8%(4)	20±8%(10)	21±9%(7)	30±6%(16)	34±8%(10)
Paco ₂ (mmHg)	36±6(28)	35±3(27)	30±6(12)	32±5(30)	35±5(16)
Art Blood Ph.	7.39±0.03(30)	7.43±0.03(18)	7.31±0.07(12)	7.47±0.08(30)	7.22±0.10(12)
PIP (Peak Inspiratory Pres) (CmH ₂ O)	—	30±4(18)	31±4(8)	36±6(32)	41±8(15)
<i>Hemodynamic</i>					
Cardiac Index (L/M ² /min)	3.6±0.3(30)	5.1±1.3(16)	3.4±1.9(9)	4.8±1.6(30)	1.9±1.0(16)
Central Venous Pres (cm H ₂ O)	5±3(21)	7±4(18)	8±4(12)	10±5(34)	16±6(18)
Pulm Art Systolic Pres (mmHg)	23±4(6)	24±3(4)	29±3(4)	36±5(9)	34±6(5)
Pulm Art Mean Pres (mmHg)	19±3(5)	22±4(6)	23±4(6)	28±5(15)	29±6(12)
Left Atrial (wedge) Pres. (mmHg)	6±2(4)	12±4(5)	5±4(4)	11±4(14)	15±3(12)
Mean Arterial Blood Pres. (mmHg)	86±10(30)	78±15(18)	73±16(12)	89±13(34)	65±10(18)

Average values ±S.D. of Mean, and (Number of Patients)

* 30 Patients

+ 27 Patients

and anaerobic cultures of bile and peritoneal fluid grew *Bacteroides*, *C. perfringens*, and *E. coli*. An endotracheal tube was left in place, and ventilatory support was continued for four days when the pulmonary shunt had decreased from 47% to 24%. At that stage the bioassay was positive for the circulating plasma factor injurious to the lung (See Table 4, Case 10). On the twelfth day a gastric hemorrhage was controlled by lavage. A second gastric hemorrhage accompanied by severe hypotension proved uncontrollable by lavage and intraarterial pituitrin infusion. A vagotomy and pyloroplasty were performed resulting in cessation of bleeding after 8.5 L blood replacement. Ventilatory support was again instituted for four days. The lung fields by x-ray gave evidence of slight edema after both episodes, but actual bronchopneumonia was never evident by x-ray. It is of interest to note the significantly greater shunt, PIP, and pulmonary vascular resistance after the septic episode than after the period of severe hemorrhagic shock.

Results

A. Mortality

Of the 27 patients who had been subjected to trauma and severe hemorrhagic hypotension, 20 survived as shown in Table 1. Ten of these 27 post shock patients later became septic at times ranging from 8 to 13 days after the initial insult. Five of the 10 died with patterns of combined respiratory and circulatory failure. Two other post shock patients not seriously infected, died of heart failure following coronary occlusion. The total of 7 deaths gives an overall mortality of 26% in the post hemorrhagic shock group.

Thirty-eight patients with severe non-thoracic sepsis were observed. Twelve were initially studied on the day

the infection was recognized. As indicated by Table 2, 30 patients were observed in the hyperdynamic circulatory state which is characteristic of those who recover (Av. maximal response CL= 4.8L/M²/min). Subsequently 10 of these patients entered the low output septic shock state. Eight others were first studied at a time when they already had low cardiac outputs. Of the 18 hypodynamic patients (Av. CI= 1.9± 1.0L/M²/min) all had significant pulmonary shunting. Twelve of the 18 died, giving an overall mortality of 31% for the septic group.

It is of interest to note that, if the 10 post shock patients who subsequently became septic are removed from the shock group and added to the septic group, the mortality in the studied patients with trauma and hemorrhagic shock is only 12% while the mortality in the severely septic group becomes 35%.

B. Clinical Pattern of Response

For comparison, the data from respiratory and hemodynamic measurements of 30 previously studied patients who made uneventful convalescence after major surgery¹⁴ are presented with those from the post hemorrhagic shock and septic patients. It should be noted that none of the patients with uneventful convalescence were given ventilator support.

1. *Post hemorrhagic shock plus trauma.* The course of a patient who had been subjected to trauma and severe hemorrhagic shock is illustrated in Fig. 1. Characteristi-

TABLE 3. *Respiratory Response to Trauma Plus Hemorrhagic Shock*

	Hepatic Lobectomy for Liver Injury				
	Day 0	Day 1	Day 2	Day 3	Day 4
Pao ₂ (FIO ₂ =1.0) mm Hg	362±110	281±97	309±60	385±70	420±54
Paco ₂ -mm Hg	33±6	37±4	43±3	30±4	40±5
Minute Ventilation-liters	13±3	12±2	11±3	13±2	13±3
Peak Inspiratory Pres.-cm H ₂ O	32±4	31±3	31±3	30±4	32±3
Fluid Intake-liters					
Blood	11.2±4.2	1.6±0.8	0.3±0.4	0.9±1.6	0.2±0.3
Colloid	1.8±0.5	1.1±0.3	0.6±0.4	0.5±0.2	0.3±0.1
Crystalloid	7.8±1.3	3.7±0.6	2.1±0.3	3.1±1.2	2.3±1.0
Total	17.8	6.4	3.0	4.5	2.9
Fluid Output					
Urine	2.1±0.7	2.8±0.6	2.2±0.8	2.7±0.4	2.2±0.6
Other	0.6±0.1	1.6±0.7	0.9±0.4	0.9±0.3	1.2±0.2
Total	2.7	4.4	3.1	3.6	3.4

Note: Numbers are Values ± S.D. of Mean

* 12 patients, 3 late deaths.

cally there is a moderate degree of shunting and little abnormality found in the x-ray of post shock patients. In those supported by a ventilator the x-ray discloses at most a slight ground glass appearance or modest evidence of pulmonary edema. Bronchopneumonia occurred in only 3 post shock patients who did not have evidence of nonthoracic infection.

The maximal degree of shunting, shown in Table 2 amounted only to $20 \pm 8\%$ and was attained between 36 and 48 hours. Typically, the patient recovering from profound hemorrhagic shock has a high cardiac index, average 5.1 ± 1.3 L/M²/min on the second day. The maximal elevation of systolic and mean pulmonary artery pressure rose to 24 ± 3 and 22 ± 4 mmHg. respectively. This modest pulmonary hypertension reflects an elevation of left atrial (wedge) pressure to 12 ± 4 mm Hg., probably associated with a moderate overexpansion of the circulating blood volume.

The data relative to fluid balance in the post shock patients who underwent hepatic lobectomy are shown in Table 3 indicate that during the operative period in addition to an average of 11.2 liters of blood, 1.8 liters of colloid and 7.8 liters of crystalloid were infused. On the first day the average urine output was 2.8 liters, the aggregate crystalloid and colloid infusion was 4.8 liters, while blood transfusion equaled the other losses. By the fourth day the total fluid output exceeded input by 0.5 liters at a time when fluid mobilization probably was beginning.

Judging by the low peak inspiratory pressure (PIP) observed (maximal average 30 ± 4 cm H₂O), when the respirator was adjusted to a tidal volume and rate adequate to maintain a relatively normal Paco₂, the loss of compliance was small. As exemplified by the course of the patient in Figure 1 and by the combined data from the

12 patients who suffered severe liver trauma shown in Figure 2, marked increases of shunting, PIP, and PA mean pressure occurred only in patients who had developed severe non-thoracic sepsis accompanied by bronchopneumonia in the later stages of their illness.

2. *Sepsis.* Characteristically, the course of the seriously septic patient, as illustrated in Figure 3, is marked by hectic fever, an elevation of cardiac output and the development of pulmonary shunting with hypoxemia, all of which tend to be maximal on the second or third day. Not infrequently the chest x-ray may remain relatively clear or at most shows evidence of mild interstitial edema by a ground glass appearance until the advent of bronchopneumonia which may develop at anytime from 2 to 10 days later (22 of the 38 septic patients).

On the day when sepsis was first recognized the average pulmonary shunt was no more than $21 \pm 9\%$ and the PIP required for ventilation was only 31 ± 4 cm H₂O in those patients who were intubated and given ventilatory support. However, as shown in Table 2 and Figure 4, in the group with high cardiac outputs there occurred a steady progression of shunting to $30 \pm 6\%$ and PIP to 36 ± 6 cm H₂O. At this stage, 18 of 30 patients had unremarkable pulmonary x-rays. At the onset the average cardiac index was 3.4 ± 1.9 rising to 4.8 ± 1.6 L/M²/min on the third day. This hyperdynamic circulatory state is accompanied by an increase of pulmonary arterial pressure from 23 ± 4 on day 1 to a maximal value of 28 ± 5 mm Hg. At the same time left atrial (wedge) pressure rose from 5 ± 4 to 11 ± 4 mm Hg, and a maximal PA pressure to 28 ± 5 mm Hg in the patients with high cardiac outputs. The peak inspiratory pressure progressively rose in this group to 36 ± 6 cm H₂O, indicating a marked loss of compliance. If bronchopneumonia occurred, as shown in chest x-rays, further loss of compliance was reflected by

TABLE 4. Relationship of Positive Plasma Bioassay and Presence of Endotoxin to Pulmonary Shunting

Patient	Diagnosis	Day	PaO ₂	Pulmonary Shunt FIO ₂	%(Est)	Plasma Endotoxin	Plasma Bioassay
Post Hemorrhagic Shock							
1	Liver trauma	0	250	1.0	20	0	0
	Hepatic lobectomy	1	206	1.0	22	+	0
		2	265	1.0	16	0	0
2	Perforation liver and vena cava	1	260	1.0	18	0	0
		2	290	1.0	17	0	0
3	Gastric ulcers hemorrhage	0	300	1.0	22	+	+
	Vagotomy pyloroplasty	1	290	1.0	26	0	+
		2	105	0.5	16	0	0
4	Duodenal ulcer bleed	1	206	1.0	23	0	0
5	Laceration mesenteric vessels	0	243	1.0	18	0	0
		1	193	1.0	20	+	0
		1	306	1.0	15	0	0
Sepsis							
1	Urinary sepsis shock	1	115	0.4	15	+	+++
		2	240	1.5	22	0	+
		3	83	0.2	8	0	0
2	Pancreatitis, peritonitis	3	68	0.2	12	0	++
		5	120	0.5	16	0	++
3	Colon obstruction	2	81	0.2	6	0	0
		3	485	1.0	5	0	0
4	Jejunal volvulus	2	98	0.5	18	+	0
5	Cirrhosis, cholangitis shock	2	96	0.5	19	0	0
		3	144	0.5	12	0	++
		7	69	0.5	22	+	++
		10	90	1.0	30	+	+
		2	45	0.5	32	0	++
6	Decubiti, septicemia	4	72	1.0	34	0	0
		2	66	0.5	28	0	0
7	Bowel infarct	4	97	0.5	20	0	0
		1	73	0.5	26	+	+
8	Corrosive jejunal necrosis and perforation	3	265	1.0	18	0	0
		5	120	0.5	16	0	0
		2	110	1.0	28		+
9	Duodenal necrosis Peritonitis, fistula	5	126	1.0	24		+
		7	312	1.0	17	0	+
		15	115	1.0	28	+	+
		18	78	1.0	32	0	0
		24	310	1.0	16	+	0
		28	72	1.0	36	0	++
10	Pancreatitis, cholangitis Subdiaphragmatic abscess	2	69	1.0	40	0	+++
		3	73	1.0	34		++
		7	102	0.7	23	+	+
		11	288	1.0	16	+	0
11	Non-occlusive gangrene Gall bladder and small bowel peritonitis	1	301	1.0	18	+	0
		2	112	1.0	28	0	++
		7	404	1.0	16	0	+
12	Cirrhosis, peritonitis	1	69	1.0	30	0	++
		3	73	1.0	34	0	+

a rise of peak inspiratory pressures to values as high as 60 cm H₂O.

In the group of patients with low cardiac output septic shock (average CI = 1.9 ± 1.0 L/M²/min) the pulmonary artery pressure was 29 ± 6 mm Hg, and left atrial (wedge) pressure was 15 ± 3 mm Hg while venous pressure was elevated on the average to 16 ± 6 cm H₂O. Pulmonary A-V shunting rose to an average of $34 \pm 8\%$, and values

up to 51% were observed prior to death. PIP on the average rose to 41 ± 8 cm H₂O. All but three gave x-ray evidence of bronchopneumonia.

C. Results of Endotoxin Assay and Bioassay

In Table 4 are given the results of the plasma assays for endotoxin and for the presence of circulating agents injurious to the lung. No correlation exists between the

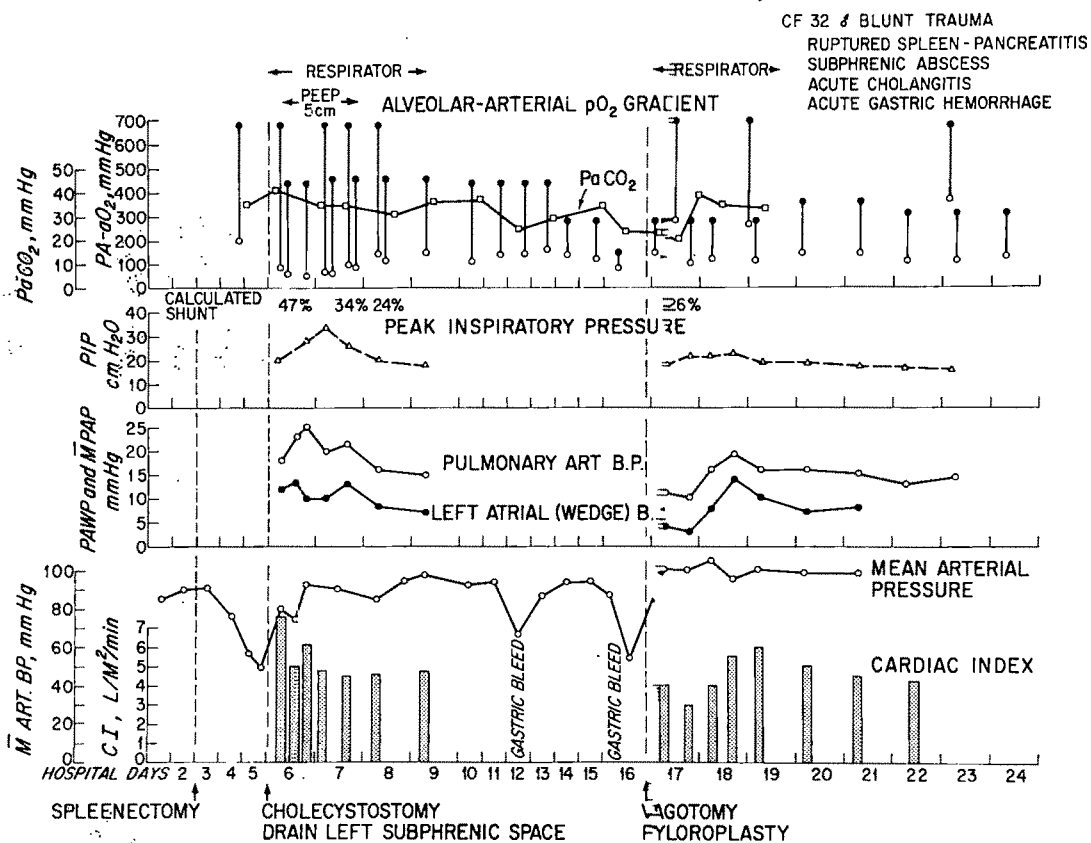


FIG. 3. The clinical course of a 32-year-old patient who developed pancreatitis and infection after splenectomy and who subsequently was in hemorrhagic shock from gastric bleeding. Note the greater pulmonary and hemodynamic effects of sepsis.

presence of endotoxin and the presence or degree of abnormal pulmonary A-V shunting in either the post shock or septic patients. On the other hand, the bioassay for the pneumonitis inducing factors was present in 9 of 12 septic patients tested, but in only one of 5 post shock patients. Inspection of the serial data in Table 4 will reveal that a positive bioassay often was present early in the septic course followed by the development of severe pulmonary shunts, only to disappear later from the plasma. No positive bioassays have been observed in testing the plasma from 5 normal people and from 8 patients who were neither septic nor post shock.

Discussion

The foregoing comparative data make it evident that the severity and duration of respiratory insufficiency is significantly greater following the onset of major non-thoracic infection than after profound hemorrhagic shock. In fact, bronchopneumonia occurred but three times in 20 post shock patients who did not otherwise become infected, and pulmonary failure was not a contributor to either of the deaths which occurred in this group. On the other hand, bronchopneumonia developed in 58% of the septic patients, and death was due to severe shunting in 83% of the septic patients who died. These findings support the views of others^{8,18,21,32} concerning the greater importance of sepsis in the induction of so called "shock

lung" in which severe shunting^{14,17,27,37} and loss of compliance and increased work of breathing^{7,30,32} are the typical clinical manifestations.

In man, pathological assessment of pulmonary lesions is difficult because of agonal changes at autopsy. However, lung biopsies at thoracotomy during hemorrhagic shock and in septic states have disclosed abnormalities^{14,17} which are reproducible in experimental animals.^{6,11,13} It appears that, regardless of the nature of the insult, the lung has essentially the same response, the formation of septal edema.¹⁶ The lesion after hemorrhagic shock is in most respects similar to the early Stage I lesion after the onset of sepsis. Clowes^{10,14} Blaisdell,⁶ and others²⁴ have reviewed the sequence of events. Characteristically the *post shock lesion* consists of septal edema, vascular congestion with trapped platelet emboli, and some alveolar collapse. The *Stage I* lesion of sepsis in addition to septal edema and vascular congestion is characterized by leucocytic infiltration and more pronounced diffuse focal alveolar collapse, referred to by Border and Gallo⁷ as focal atelectasis. Clinically the *Stage I* lesion is manifested by hypoxemia and shunting in the presence of clear or only a slight ground glass appearance of the lung fields by x-ray. Vito et al.³⁷ were impressed by the fact that considerable edema, present in the lungs at autopsy of their septic patients, averaged 688 grams per square meter of body surface area, despite

the absence of x-ray abnormalities in the majority. If unchecked, the lung lesion may progress on to *Stage II*, the typical bronchopneumonia with polymorphonuclear leucocytes in the alveoli and septa accompanied by areas of consolidation, which are recognizable by the mottled appearance of the pulmonary x-ray. Experimentally it has been found both in post shock states and in sepsis that both synthesis and secretion of surfactant, principally L-dipalmitoyl phosphatidyl choline, are reduced.¹⁴ Surfactant action is further impaired by the presence in the alveoli of protein which inhibits the surface activity of the phospholipids. Not only do these effects promote alveolar collapse, but the loss of ciliary action and the bacteriostatic activity of surfactant may contribute to the advent of bronchopneumonia.

If the clinical manifestations of *post shock pneumonitis* and the early *Stage I* pneumonitis at the onset of sepsis be compared, there are no significant differences in the various parameters examined in Table 2 and Figure 4. In this respect, it must be pointed out that all the patients studied were supported by a ventilator at the height of their respiratory dysfunction. In all of the post shock and septic patients of this group who were operated upon, the endotracheal tube was left in place for continued ventilation by a volume controlled respirator. Under these conditions the shunt, in the entire group of postshock patients who were studied, declined from a maximal average value of $20 \pm 8\%$ at 36 hours to $12 \pm 6\%$ on the fourth day. Only those who became secondarily infected developed severe hypoxemia and shunts as illustrated by Figures 1 and 2. However, the extent of shunting in the septic patients was significantly greater from the second day onward, even when the patients' lesions remained in the *Stage I*. The average maximal value was $30 \pm 6\%$ on the third day. It is also apparent that even in the absence of bronchopneumonia the shunt usually does not subside fully until the septic focus is eliminated. Of course, in those who developed bronchopneumonia, *Stage II*, the degree of shunting reached much greater values, which is illustrated by the average of $34 \pm 8\%$ in the patients in the low output state, all but one of whom gave evidence of bronchopneumonia.

A close relationship ($r = 0.82$) exists between the degree of venous admixture and the peak inspiratory pressure required to ventilate the lung sufficiently to maintain P_{aCO_2} values in the low normal range. It thus, becomes evident from this apparent loss of compliance that edema and alveolar collapse of the lung must be significantly greater in the *Stage I* lesion of sepsis than that encountered after shock.

One cannot entirely separate lung function from the performance of other vital systems in relation to the economy of the body as a whole. Principal among these function is that of the cardiovascular system. Siegal

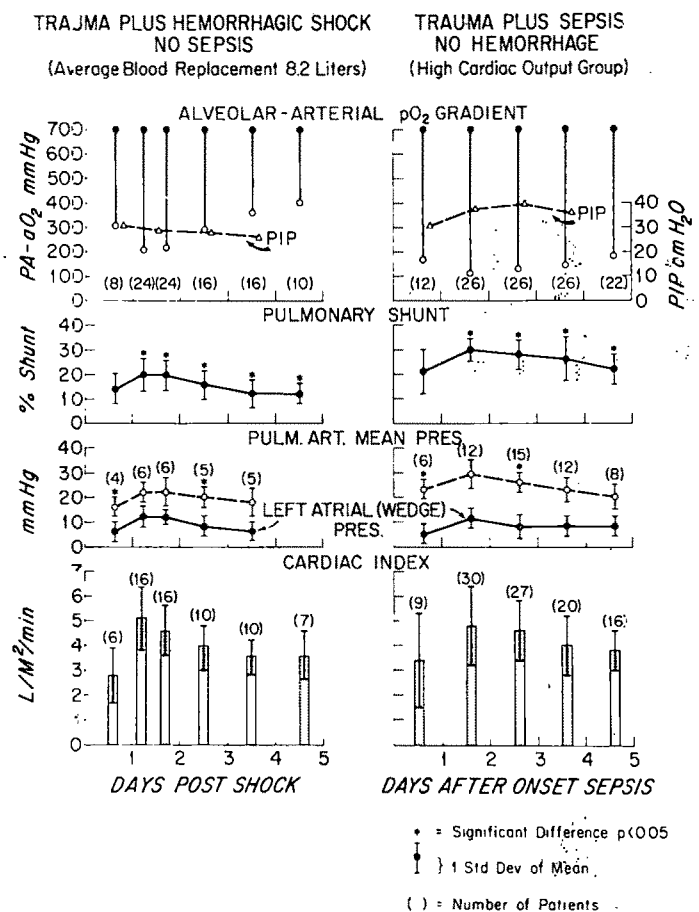


FIG. 4. A comparison of the severity of pulmonary shunt, loss of compliance, and hemodynamic abnormalities in postshock and septic patients. Attention is drawn to the significantly greater pulmonary arterial pressure and pulmonary vascular resistance which accompany the elevated peak inspiratory pressures in the septic patients.

et al.,³⁵ using mixing time of dye in the central circulation as an indicator of cardiovascular dysfunction, have noted a close correlation with the veno-arterial admixture. Support for this concept is found in these results. Cardiac function was excellent in the majority of postshock patients when they survived the operation. The postoperative cardiac indices were high (average $52/M^2/min$) but subsided quickly to near normal values by the fourth day. On the other hand, only 20 of the 38 septic patients successfully maintained a high cardiac output throughout their clinical course in response to the characteristic low peripheral vascular resistance.^{14,34} Those who failed to do so (Table 2) also exhibited the greatest degree of shunting and loss of compliance. Three principal causes of circulatory insufficiency in sepsis are suggested: 1) fluid translocation and hypovolemia, 2) increased pulmonary vascular resistance with right heart failure,¹¹ and 3) biventricular failure.³⁹ The first is usually corrected, but high central venous pressures, characteristic of right heart failure are common in severely septic patients³⁷ (Table 2). That elevation of pulmonary vascular resis-

tance plays a major role in the right heart failure of sepsis and not in the post shock state is shown by the high mean pulmonary arterial pressures of 28 ± 5 and 29 ± 6 mm Hg respectively in the high and low output septic patients. There is also a significantly greater gradient from mean PA pressure to left atrial pressure in the septic than in the postshock patients. As observed by a number of investigators,^{23,34,35} the cardiac output itself is related to the degree of shunting. It is striking how shunt becomes reduced as the cardiac output improves when myocardial failure responds to inotropic agents or to glucose, potassium, and insulin therapy.³⁹ This is illustrated by comparison of the patients with low cardiac output and those with high output. The latter part of the patient's course in Figure 1 is also illustrative. Thus, it appears that the greater shunting, loss of compliance, and pulmonary vascular resistance are all greater and last longer in the septic state than after severe hemorrhagic shock with massive blood replacement. The presence of greater shunting in the septic patients argues that more non-ventilated or poorly ventilated alveoli are being perfused than in the post shock patients.⁴⁰ This concept, plus the greater reduction of compliance indicates that focal alveolar collapse and interstitial edema, are principally responsible for these changes which appear to be significantly greater in sepsis, even more so if bronchopneumonia is present. Probably the normal recruitment of pulmonary capillaries, as cardiac output increases, is accomplished by overcoming the critical closing pressure. It appears that edema and other factors may be responsible for a reduction of functional residual capacity and for a greater critical closing pressures in the lungs of septic patients, leading to the greater pulmonary arterial pressures and perfusion pressure gradients found in sepsis.²⁹

Etiology. Since the lung responds by edema to a variety of insults, it is possible that different etiological agents are responsible for the pulmonary dysfunction that occurs in the post shock and septic patients. In the former a number of suggestions have been made. MacNamara et al.²⁵ have demonstrated that micro clots from transferred blood may accumulate in the lung. Platelets trapped by the lung may release serotonin and other substances.² Clots may be lysed to release fibrinopeptides. All are known to cause a rise in pulmonary vascular resistance and to increase capillary permeability. Moss et al.²⁸ have proposed that cerebral ischemia results in pulmonary vasoconstriction.

The experimental and clinical evidence for possible etiological circulating agents responsible for pneumonitis in nonthoracic sepsis have recently been reviewed by Clowes.¹⁴ These include: 1) endotoxin,²² 2) fibrinopeptides secondary to diffuse intravascular coagulation (DIC) and activation of plasmin, both through activated Factor XII, 3) kinins, 4) serotonin, prostaglandins, and ATP from platelets, and 5) vasoactive peptides released

from lysis of protein from damaged tissues. Although space does not permit a complete discussion of the pros and cons of each, the results of the endotoxin assay given in Table 4 suggest that, in man, endotoxin in the concentrations present in the plasma of septic patients does not react directly with the lung. However, one must not overlook the fact that endotoxin is taken up by the RE system which is particularly active in the lung. There it may destroy macrophages which release proteolytic lysozymal enzymes capable of activating a wide variety of vasoactive peptides. On the other hand, the results of the bioassay for toxic substances which have molecular weights between 1,000 and 10,000 (not endotoxin) strongly suggest that the septic patients have one or more agents circulating which are capable of inducing pulmonary edema and rise of pulmonary vascular resistance. Although the numbers were small, only 20% of the post shock patients gave evidence of these agents being present in the plasma while they were present in 75% of the septic patients. Furthermore, their presence seemed to precede the development of A-V shunting, edema and reduced compliance in the septic patients. Whatever the cause of the pulmonary hemodynamic and respiratory abnormalities in the post-hemorrhagic shock state, it is evident that they are neither as severe nor as long lasting as in the septic state;

Therapeutic conclusions. To obtain the optimal physiological state for survival and recovery the respiratory, circulatory, and metabolic abnormalities must all be considered. Furthermore, it is of great importance to recognize the effect that the malfunction of one has on the function of the others.³⁵ Since pulmonary insufficiency is secondary to trauma accompanied either by hemorrhagic shock or by sepsis, attention here will be devoted principally to maintenance of respiratory function and to its restoration should serious loss of pulmonary ventilation or gas exchange supervene.

The volume controlled ventilator, used to assure tidal volume and rate adequate to maintain P_{aCO_2} at or slightly below normal, is capable of preventing a reduction of functional residual capacity (FRC). As alveoli collapse secondary to edema formation and loss of surfactant secretion, FRC may fall from the normal adult value of 2 to 2.5 l to 1 l accompanied by increase of venous admixture and in the work of breathing.³⁰ The excellent recovery of lung function in the early postoperative period attests to the value of this form of preventive therapy in the patients who undergoes hepatic lobectomy and massive blood replacement. Also the fact that 42% of the septic patients did not progress beyond the Stage I of pneumonitis and did not reveal evidence of bronchopneumonia by x-ray further supports this view. Although the early use of respirators in this series did not prevent some degree of post shock pneumonitis or the Stage I pneumonitis of sepsis, the severity and incidence of

bronchopneumonia was less than in previously studied series by Clowes et al.^{10,11} Failing improvement of shunting, positive end-expiratory pressure (PEEP) is of value in reduction of alveolar collapse and restoration of a more normal ventilation perfusion ratio as shown in Figures 1 and 3. Dangers exist in its use. Venous return may be reduced and pulmonary capillary resistance may rise accompanied by a fall of cardiac output if excessive PEEP is employed.³¹ Without monitoring of the pulmonary hemodynamics and cardiac output, PEEP in excess of 15 cm H₂O should not be employed.

As shown by Siegal et al.,³⁵ not only does the metabolic state of the patient deteriorate with a combined fall of cardiorespiratory function, but the per cent of venous admixture increases. Pao₂ further declines, and a vicious cycle may be induced. The data presented here show that such a situation is more liable to occur in the presence of sepsis. For these reasons other measures to sustain a cardiac output sufficient to meet circulatory demands by the periphery are of equal importance. These include adequate but not excessive fluid replacement and inotropic agents such as isoproterenol.²³ More recently excellent results have been obtained in low output septic patients by administration of glucose, potassium and insulin in which a reduction of both shunt and pulmonary vascular resistance accompanied an increase of cardiac output.¹²

The respirator itself may play a role in improvement of the circulation. Not only does it help to improve compliance by keeping alveoli from collapsing or by assisting in the reexpansion of those already collapsed, but it may relieve the patient of the work of breathing when well regulated. Thus, the large circulatory demand for perfusing the overworked muscles of respiration may be in part eliminated. At the same time as alveoli are reexpanded the resistance to blood flow in the capillaries around them it appears to be reduced. (Fig. 4). In both the post shock and septic states as PIP and pulmonary shunt were reduced the pulmonary artery pressure and gradient of pressure to the left atrium declined.

Although abnormal pulmonary capillary permeability appears to be a feature of the early formation of edema and pneumonitis after shock and sepsis, the use of intravenous crystalloid solution may or may not be detrimental. The data in Table 3 on fluid balance suggest that shunt in the post hemorrhagic shock state may be related to this therapy, since the shunt appears to decrease as fluid excretion increases. However, there are so many variables present that this study does not settle this issue. The use of colloid has been debated in resuscitation of shock. Yet an analysis of colloid input as shown in Table 3 has indicated that, contrary to the usual belief, there was an inverse relationship of shunt percentage to the amount of colloid infused.

Many other factors contribute to the maintenance of

pulmonary function, especially in the prolonged septic course. Among the more important is protein nutrition for antibacterial defense and continued surfactant synthesis.^{1,5} Without adequate function of all vital systems no amount of respiratory support will prevent pulmonary failure and death. Finally, the most important measure contributing to the resolution of pneumonitis is elimination of gangrenous tissue and the septic focus.

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DISCUSSION

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): The concept of post-traumatic respiratory insufficiency is one that all of us have lived with for a distressing time, and it has become, I think, clearly recognized that the final common pathway through which so many of our complex surgical patients or badly injured individuals pass. I think Dr. Clowes has continued, both in the laboratory and in his clinical investigations, to show that the pathogenesis of PTRI based upon degree of shock, crystalloid solution, colloid solution, or what not, is a myth. The critical factor in the genesis of posttraumatic respiratory insufficiency is infection occurring either in the lung or in other spots.

The work he was kind enough to allude to, developed on our service by Bob Fulton and Cal Jones, I think, is rather clear, and I'd like to share with you a few bits of data from it.

(Slide) This points out all of the mythical factors that have been discussed with great heat and very little light in the last four years about the pathogenesis of posttraumatic respiratory insufficiency.

(Slide) If one analyses a large number of clinical patients ill of respiratory failure, one finds unequivocally that the factor of greatest significance in the development of posttraumatic respiratory insufficiency is *not* these factors, which we can show with pure group analysis of some 500 patients cared for directly on our service. Sepsis is the overriding single factor involved in the pathogenesis of posttraumatic respiratory insufficiency.

So in this sense we would like to thoroughly agree with the essayist that the cause in most situations, in most practical patient care opportunities today, is entirely that of infection being the cause of post-traumatic respiratory insufficiency, and it will persist until that infection is treated effectively.

I think the treatment is entirely another subject, but indicates that this posttraumatic respiratory insufficiency will continue until the septic process itself is treated. This usually requires mechanical treatment, not reliance on antibiotics alone.

I would, in closing, only make one point of difference with Dr.

Clowes. If you follow the very thoughtful work that has developed from our service in the last years by Dr. Truman Mays, hepatic lobectomy for major hepatic trauma has gone its way as an aspect of modern medical practice, and should ordinarily be replaced in most patients by hepatic artery ligation.

DR. GEORGE H. A. CLOWES, JR. (Closing discussion): I appreciate very much Dr. Polk's remarks. He has been one of the people who really have taken the trouble to analyze the cause and effect of many of the difficulties that we encounter in the postoperative care of patients.

I want to say another word to draw to your attention a very fine issue of the *Surgical Clinics of North America*, that Watts Web has edited. It came out in October with a series of articles in it on respiratory problems in surgery. The interesting thing to me is that the title "shock lung" is never used in that issue. It is referred to obliquely in some of the articles. "Shock lung" is an entity associated with tissue injury and sepsis and should not be used because of the suggestion that shock is principally responsible.

I would suggest that we really ought to invent some terms such as "posttraumatic lung" or perhaps the term that Ben Eiseman has suggested for his paper "posttraumatic adult respiratory distress syndrome." We need some other term. "Shock" is overemphasized.

And finally, I want to add just one little word about the bioassay which demonstrates a substance in the blood of humans, when they are injured and septic, capable of inducing injury, edema, and pulmonary hypertension in perfused rabbit lungs. Only one of six patients was positive in the postshock state. It is even questionable if he wasn't septic at that time. Nine of 12 were positive in the septic state, and there was a close correlation with the degree of shunting in the early stage of its development. Endotoxin assay by the *Limulus* lysate assay disclosed that endotoxin concentration did not correlate with the development of the pulmonary lesion.

Therefore, I think that we are looking at a circulating agent probably a peptide or prostaglandin which is responsible for much of this respiratory difficulty in the presence of sepsis in trauma.

The Changing Pattern of Post-traumatic Respiratory Distress Syndrome

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During a one year period, 78 patients at the Denver General Hospital required mechanical ventilation following injury. Thirteen patients were judged to have Respiratory Distress Syndrome. Of these, 9 had classic early onset RDS but, with intravenous fluid restriction following resuscitation, diuretics and careful mechanical ventilation, all recovered. Six patients, all of whom were septic, developed late onset RDS 5 or more days after injury; 5 died. Disparity between early and late onset RDS is emphasized; the one with good, the other with dismal prognosis. The current need is to improve treatment of late onset RDS, which frequently is associated with bacterial infection.

POST-TRAUMATIC respiratory distress syndrome (RDS) came into explosive prominence during management of combat casualties in the Vietnam War.^{13,18,22,25-27} Since then an enormous volume of literature has evolved concerning its pathogenesis, recognition and care.^{4,6,8} Main emphasis has remained, as during the War, on development of respiratory failure in the immediate post-injury period associating the syndrome with chest wall contusion,²² blast,²¹ multiple blood transfusions,^{10,19} fat embolism,^{2,12} aspiration,⁵ shock,⁹ cerebral hypoxia, and fluid and sodium overload.²⁶ In a series of classic articles, Ashbaugh^{1,3,18,23} described the adult respiratory syndrome and later reviewed experience with 31 patients who died of the lesion, 19 of whom had pulmonary sepsis. He emphasized that infection complicated prolonged ventilation.

As part of our interest in developing a membrane oxygenator to provide prolonged ventilatory support in RDS we reviewed the pattern of post-trauma RDS over a one-year period. Our aim was to define indications for this technique which is now technically feasible.^{7,15-17}

In this paper we show that pulmonary insufficiency in the immediate post-injury period if treated vigorously is not usually fatal. Instead, RDS of late onset associated

with generalized or pulmonary sepsis is the important life-threatening lesion toward which prolonged oxygenator support will have to be directed.

Clinical Experience

During the period of January 1, 1973 to January 1, 1974, 78 patients at the Denver General Hospital were administered endotracheal mechanical ventilation following injury. This amounted to approximately 14% of all patients operated upon for major trauma during this period. Situated in the center of the city and served by efficient police-dispatched ambulances, we received many severely wounded who would have expired under less ideal emergency care systems.

Denver is 5,280 feet above sea level. Arterial pO_2 is 74mmHg in a normal person breathing room air. There is, therefore, a slight but appreciable decrease in ventilatory reserve that may make the patient more prone to RDS at this altitude than at sea level.

The mean age of these 78 injured patients requiring ventilatory support was 39 years, with a range of 16-81 years. Sixty-nine patients were males and 9 were females.

Hospital death rate was 44% (34/78), but only 5 (6%) of these patients died primarily of pulmonary insufficiency. Table 1 shows the cause of death. The 5 pulmonary deaths represent 15% of the total deaths. Twenty-two (64%) were due to brain injury; two (6%) to hepatorenal failure; three (9%) to septic shock, one (3%) to cardiac failure, and another to exsanguination (3%). As emphasized by Moore,²⁶ the greatest killer is late secondary organ (heart, lung, liver and kidney) failure.

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TABLE 1. Cause of Deaths: 34 Patients
(44% of Patients Ventilated)

	# Patients	%
Brain Injury	22	64%
Pulmonary Insufficiency	5	15%
Septic Shock	3	9%
Hepato-renal Failure	2	6%
Cardiac Failure	1	3%
Exsanguination	1	3%
Total	34	100%

Types of Injury in Patients Requiring Mechanical Ventilation

Head Injury. Brain swelling, the characteristic final common pathway to death following head injury, is potentiated by hypoxia and hypercarbia. We believe assisted mechanical ventilation is accepted neurosurgical treatment in such patients.²⁸ Of the 78 total patients, 31 (39%) suffered head injury, often in association with other trauma. Twenty patients had closed head injury and 11 had open injuries. The mortality in these severe head injury patients was 71%, but only two (6%) of these deaths were due to respiratory failure. Neither of the dying patients had ventilatory problems in the immediate post-injury period. Both suffered closed head trauma and both apparently were recovering from their brain injury with recession of unconsciousness when pulmonary sepsis intervened and they died of pulmonary insufficiency 19 and 21 days following injury.

Thoracic Injury. During this 12-month period we cared for 140 patients with major thoracic trauma. Sixteen patients required thoracotomy (14%); 10 for pericardial tamponade or actively bleeding cardiac wounds; 5 for massive intrathoracic bleeding; and one as a part of other resuscitative efforts. All 16 patients required postoperative ventilation, but only 3 thoracotomy patients de-

TABLE 2. Early Onset RDS: 9 Patients
(11.5% of patients ventilated)

Injury	Day Onset RDS	Duration	Etiology
1. Extremity fracture	2	3	Fat embolus
2. Avulsion arm	2	4	Shock
3. Blunt chest trauma	1	3	Pulmonary contusion
4. Blunt chest trauma	1	2	Pulmonary contusion
5. Blunt chest trauma	1	2	Pulmonary contusion
6. Flail chest	1	4	Pulmonary contusion
7. Flail chest*	1	5	Pulmonary contusion
8. GSW heart	1	4	Shock
9. Stab (lung, liver, internal mammary artery)**	1	5	Shock

*Recovered from initial RDS—sepsis, pneumonia 2-3 weeks later; died with late onset RDS.

**Early onset RDS resolved—then pneumonia—lived after 30 days on ventilator.

veloped significant RDS. There were no deaths ascribable to the RDS.

Six patients were mechanically respired for a mean of 14 days for flail chest. Two flail chest patients had florid RDS secondary to pulmonary contusion. One was ventilated 14 days but by the day 4 post-injury his RDS had cleared and ventilatory support was maintained until his chest wall stabilized and he recovered. The other patient with a flail chest similarly recovered from his early RDS but after 2 weeks, while still on the respirator, developed complicating sepsis and died on 43 days post-injury.

Six other patients had pulmonary contusion secondary to blunt trauma, and 3 developed RDS immediately after injury. They were mechanically ventilated a mean of only 2 days. Characteristically their acute symptoms and alarming roentgenologic findings cleared promptly under our current regime of adequate ventilation, fluid restriction and diuretics after the initial period of resuscitation.

Abdominal Injury. None of the 14 patients requiring mechanical ventilation following major vascular or abdominal injury developed RDS. A number of these injured patients bled from stress ulcer associated with intraabdominal sepsis,²⁹ but in them the stomach, not the lung, was the secondary target organ.

Extremity and Spine Injuries. Despite the large number of extremity injuries cared for by our Orthopedic Division (350 annually), only two patients, solely with extremity injuries, developed RDS sufficiently severe to require mechanical ventilation. One patient had classic fat embolism, requiring mechanical ventilation for 4 days.

Another patient with a fractured hip and chronic lung disease developed late (day 6 post-injury) respiratory insufficiency and died on day 19 post-injury of Klebsiella pneumonia. Postmortem showed evidence of multiple focal pulmonary emboli but the predominant process was bronchopneumonia.

Burns. Two patients with extensive burns were ventilated. Neither had inhalation burns. One died on the 21st post-burn day of liver and kidney failure. The other died on the 40th post-burn day in bacteremic hypotension and had severe RDS.

Early vs. Late Onset RDS

Two distinct patterns of RDS are discernible in this experience. They are so disparate as to represent two separate diseases or syndromes.

Early Onset RDS becomes manifest within hours after injury. Its course, though clearly life-threatening by reason of severely impaired blood oxygenation, is self-limited.

As shown in Table 2, 9 patients developed respiratory insufficiency within 12 hours after injury and were categorized as suffering early onset RDS. Causes of injury were (1) blunt chest trauma (5); (1) GSW or stab of chest (2); avulsion of arm and exsanguination, and fat

TABLE 3. Late Onset RDS: 5 Patients
(6.4% of patients ventilated)

Injury	Day Onset RDS	Dura- tion	Etiology
1. Flail chest	14	29	Sepsis
2. Fractured hip	5	13	COPD & pneumonia
3. Burn (50%)	23	17	Aspiration pneumonia
4. Blunt head injury	9	10	Pneumonia
5. Blunt head injury	5	12	Pneumonia

embolism. Although all of these patients demonstrated the classic clinical, roentgenologic and blood gas abnormalities associated with RDS,²³ all recovered from their initial respiratory distress. One patient exsanguinated and had a cardiac arrest from avulsion of his arm by a conveyor belt prior to Emergency Department admission. He was resuscitated but was judged neurologically dead 4 days later. At autopsy his lungs were edematous, although this was not the cause of his death.

A second patient, stabbed in the internal mammary artery, lung and liver, was recovering from early onset RDS when on the 8th post-injury day she developed pneumonia and her RDS worsened. She required a total of 30 days of mechanical ventilation and after a long and complicated course she recovered. She thus showed manifestation of both early and late onset RDS.

Late Onset RDS. Six patients developed respiratory insufficiency 5 or more days after injury. One patient had experienced early onset respiratory distress prior to that time. As detailed in Table 3, each had significant pulmonary sepsis associated with the respiratory distress and 5 of the 6 died. Late onset, sepsis and death were the apocalyptic triad. The inexorable clinical course was progressive respiratory insufficiency, requiring increasing concentrations of $F_{I}O_2$ and pressures to ventilate the non-compliant lung before the patient died of pulmonary insufficiency or bacteremic hypotension.

Case Reports

Case I. A 71-year-old man with known severe coronary disease sustained a flail chest and questioned myocardial contusion in an automobile accident. His pulmonary insufficiency was controlled early in the immediate post-injury period with a volume respirator and judicious use of intravenous fluids and diuretics. Two weeks following injury, while still on the respirator awaiting final stabilization of his chest wall, he asked to be and was transferred to another hospital. He developed gradual renal failure, bilateral pneumonia, generalized sepsis, and then underwent cholecystectomy. He died in respiratory failure and generalized sepsis 43 days after injury.

Case II. A 64-year-old housewife with known chronic obstructive disease fell and fractured her femur. Five days later she developed Klebsiella pneumonia, which was controlled with Keflin and Kanomycin. There was no clinical evidence of thrombophlebitis or pulmonary embolism. She died a septic and pulmonary death on the 18th post-injury day after onset of her respiratory syndrome.

Case III. A 40-year-old man suffered 50% third-degree burns. Despite partial skin graft coverage, he became septic and on the 23rd post-burn day vomited and aspirated stomach contents. He developed progressive bilateral pneumonia and required mechanical ventilation with increasing concentrations of oxygen. He died of respiratory insufficiency and sepsis 17 days after aspiration and 40 days after being burned.

Case IV. A 52-year-old alcoholic man suffered a closed head injury in a fall. On the 5th post-injury day his sputum grew Klebsiella and *D. pneumoniae* and he was treated with chloramphenicol. On day 9 post-injury he underwent craniotomy for intercerebral bleeding with good neurological result. Despite vigorous pulmonary hygiene and further antibiotic therapy with colistin and gentamycin, progressive pulmonary insufficiency caused his death 10 days postoperative. Mechanical ventilation with 100% $F_{I}O_2$ and positive end expiratory pressure of 5-10mm H_2O were to no avail.

Case V. A 43-year-old alcoholic man underwent surgery immediately following emergency admission for subdural and epidural hematomas caused by blunt head trauma. On day 5 postoperative his sputum grew *D. pneumoniae* and penicillin therapy was begun. With progression of disease oxacillin and gentomycin were added. Response was poor and progressive respiratory insufficiency made mechanical respiration with 100% $F_{I}O_2$ mandatory. Despite vigorous treatment, he died 17 days postoperative of respiratory failure.

Discussion

The pattern of post-injury RDS has changed since it demanded such intense interest a few years ago during the Vietnam War. Respiratory insufficiency occurring immediately following injury still exists, but compulsive attention to fluid therapy, diuretics and adequate mechanical ventilation has aborted many attacks and has removed the life-threatening sting from many others. None of our patients in this busy trauma center died from early onset RDS during this 12-month period.

Our routine for management of patients at risk for post-injury RDS is not unique, save for meticulous attention to respiratory care in the few days immediately following injury. Three large caliber intravenous catheters are inserted while the patient is in the Emergency Department and Ringer's Lactate is given as required to

maintain satisfactory peripheral perfusion for the 15-30 minutes before cross-matched ACD blood becomes available. Whenever possible a millipore filter is used and changed with every 3rd unit. CVP is monitored via a subclavian or jugular vein. As soon as hemostasis is achieved, fluid and blood infusion is sharply limited and 20mg Furosamide (Lasix) is given and repeated as required. We do not wait for signs of RDS to develop, preferring the easier path of aborting the attack by fluid restriction. When there is major suspicion of pulmonary contusion, salt-poor albumin is occasionally used for resuscitation along with blood. Mechanical ventilation is initiated early via a cuffed endotracheal tube with early disregard for potential oxygen toxicity. Within a few hours $F_{I}O_2$ can be decreased to levels that will support arterial pO_2 of 70-100 mmHg. In the early post-injury hours, pulmonary capillary hypoxia is more threatening for subsequent RDS than is oxygen toxicity. Positive end expiratory pressure (PEEP) is used when the RDS is severe.

None of these principles or techniques is original but in the aggregate have, as the current experience typifies, minimized the threat of early onset post-injury RDS. None of our clinical series died of post-injury RDS.

Late onset RDS is in complete contrast in timing, etiology, resistance to mechanical ventilation and prognosis. We described 5 deaths: none had severe ventilatory problems in the immediate post-injury period. Common to them was sepsis, which could have been primary or a complication to other pulmonary problems. Identifiable factors in etiology are aspiration, bacterial pneumonia secondary to prolonged mechanical ventilation, pulmonary embolism (unproven in this series) and the pulmonary effects of generalized bacteremia. Multiple organ failure including the heart, kidneys and liver influences the lungs.

The precise mechanism by which bacteremia depresses pulmonary function is not known. Endotoxin, with its release of vasoactive amines causes increased pulmonary capillary permeability, which may play a part.¹¹ So too may the multiple microemboli associated with *E. coli* bacteremia.¹⁴ Sepsis decreases synthesis of surfactant²⁴ which also may be of importance. Whatever the explanation, both generalized and pulmonic infection are associated with late onset RDS; and antibiotics are relatively ineffective in reversing the lesion.

Ashbaugh and Petty,³ in a classic study of 51 patients with RDS, found sepsis in 36, of whom 25 died. Although their patients were not all post-injury, they emphasized the threat of infection during prolonged ventilatory assistance. Our current study with the injured confirms their thesis and, in addition, emphasizes the need to define why patients develop RDS with sepsis in the late post-injury period.

The original purpose of this study was to delineate the indications for prolonged membrane oxygenator support for post-injury RDS. They obviously are few. An occasional patient will probably benefit from prolonged membrane oxygenator support in the first few days following injury. For the most part this will be limited to the aged and to those with severe underlying lung disease.

The majority of candidates for oxygenator support will be those with late onset RDS associated with systemic or pulmonary sepsis. In patients who are otherwise salvageable and who do not have irreversible pulmonary fibrotic changes, prolonged oxygenation must be evaluated.

Intensive study of the cause, early diagnosis and prevention of early onset post-injury RDS has resulted in decreased incidence and improved salvage. It is now time to focus attention on the late onset analogue which still carries a fearful mortality.

Conclusions

A one year experience with 78 post-injury patients who required mechanical ventilatory support has been reviewed. Of the 13 patients judged to have RDS, 9 had classic early onset, but with fluid restriction following resuscitation, diuretics and careful mechanical ventilation, none died of early onset RDS. Five of the 6 patients who had late onset RDS died. All were septic. Disparity between the two types of RDS must be recognized. Late onset RDS provides the potential patient source for prolonged membrane oxygenator assistance.

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DISCUSSION

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): I rise to strongly reemphasize everything that Dr. Eiseman has said. I think he's right on target about the pathogenesis of this illness, despite all of our misunderstood discussions of the last couple of years. His thesis is precisely consistent with the one that was developed by Bob Fulton and Cal Jones and presented from our Department at the College about six weeks ago and will be published in *SG&O* in February.

I would like to show some slides that underline each of these points rather clearly. (Slide) In a slightly larger series of patients treated in a slightly briefer period of time, we showed that there is a variable frequency of posttraumatic respiratory insufficiency associated with a variety of illnesses that we had earlier thought had been absolutely necessary for the ultimate development of such abnormalities.

(Slide) If you look at this large group of patients to clean out the "pure" group comparisons of etiologic factors, you find a number of things: that sepsis is infinitely more significant than multiple system injury; secondly, that massive fluid therapy is of small significance compared to sepsis; and that oligemic shock itself is very slightly significant compared to the development of sepsis of some sort or another.

You see not only by the P values, but the calculation of the power of the test, that this is extremely likely to be an accurate observation. Once more, these represent civilian victims of trauma, just as Dr. Eiseman has described.

The ultimate question to be asked, though, is: Which is the chicken, and which is the egg? Does the sepsis precede the respiratory failure, or

is the respiratory failure a consequence of initial respiratory support with superimposed infection on a foreign body?

(Slide) Just as Dr. Eiseman has developed a very cogent discussion of the differential onset of the illness, I think you can see here that almost all of our patients developed posttraumatic respiratory insufficiency due to sepsis in the circumstance in which the sepsis preceded respiratory support. As a matter of fact, very infrequently did the causative events occur in the reverse relationship.

The point that Dr. Eiseman has raised is very clear, and another point, by inference, that he made is that the supportive care of an individual who is ill of respiratory distress syndrome due to sepsis with continued respiratory support is actually very unprofitable. The only chance that these individuals stand to recover from their illness is correction of the underlying sepsis.

DR. BEN EISEMAN (Closing discussion): I appreciate Dr. Polk's remarks. A few weeks ago, while Visiting Professor at Louisville, Dr. Jones and I found, by chance, the similarity of our findings and conclusions.

In our own experience, most of the sepsis proceeded late, but not early, post injury RDS. Why bacterial infection has such action on the lung I don't know, but we are currently exploring the mechanisms. Very likely they are those that similarly injure the liver causing liver failure or stomach stress ulcer.

Whatever the cause, the clinical corollary is obvious. Patients with pus as the possible cause of RDS (or hepatic coma or stress ulcer) are often too sick *not* to operate on. It may be the only chance to cure the RDS or other organ failure due to generalized bacteremia.

Ubi pus ibi evacua still pertains.

The Influence of Diet on Response to Hemorrhagic Shock

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Prior nutrition is known to influence tolerance to hypovolemic shock. This study was undertaken to determine the influence of dietary composition on the response of animals subjected to hypovolemic shock. Particular attention was directed to the role of high and low protein diet content with a proportionate change in carbohydrate content to yield isocaloric diets. Rats were placed on one of three diets and were subsequently subjected to shock either by 1) hemorrhage to a pre-determined mean arterial blood pressure, or by 2) hemorrhage of a pre-determined volume of blood based on per cent of body weight. Serial measurements were made of blood pressure, blood volume removed, survival time, hematocrit, blood glucose, pH and blood gases. The results indicate that a high protein diet does not prolong tolerance to recurrent blood loss but there is a greatly reduced tolerance to hemorrhagic shock in rats whose body weight was maintained on a low protein/high carbohydrate diet. The latter animals also exhibited impaired refill of plasma volume and a paradoxical, continuing hyperglycemic response during hypovolemia. This study suggests that although an abundant supply of blood glucose is available as an energy source, glucose uptake in the peripheral tissues is inhibited during hypovolemia by unknown mechanisms and thus homeostasis is curtailed. The protein content of the diet may be a critical factor in carbohydrate use during shock.

PRIOR NUTRITION is known to influence tolerance to hypovolemic shock. In 1942, Elman⁷ found that animals fed a high protein diet consisting of horse meat survived longer when subjected to repeated hemorrhage than dogs fed a normal or non-protein diet. In Pareira's study¹⁷ starved rats in tourniquet-induced shock exhibited a mortality rate that correlated with the degree of pre-shock weight loss. Strawitz¹⁹ concluded that severely fasted rats with depleted hepatic glycogen were less tolerant to hemorrhagic shock than well nourished rats and

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frequently developed hypoglycemia before they died. Our previous studies of this problem demonstrate that infusion of a bolus of hypertonic glucose, after hypovolemia had reached the stage of physiological decompensation, would extend survival time beyond that of control animals.¹⁶

In preparing experimental diets to study the influence of protein on response to stress there has been a tendency to regard carbohydrates simply as a supplementary component to provide calories. The wisdom of maintaining a positive protein balance before and after surgery has been debated extensively while the possible disadvantage of providing the bulk of calories as carbohydrate has been largely ignored. Yet, kwashiorkor in children is precisely such a clinical condition in which a high intake of carbohydrate is associated with a deficiency of protein, but with a caloric intake that is adequate to maintain or even increase body weight.² This study was undertaken to determine the influence of dietary composition on the response of animals subjected to the acute stress of hypovolemic shock with particular attention directed to the role of high and low protein content in which a proportionate change in carbohydrate content gave an isocaloric diet.

Methods

Growing male Sprague-Dawley rats were placed on one of three diets (Table 1). The Charles River Original Formula Diet was used as the Control (C) diet. It contained a mixture of grains, soy bean, and corn as the source of carbohydrate, analyzed as N-free extract. Due to a relatively high content of water (13%), the quantity of nutrient per 100 g of diet was less than that in the test

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TABLE 1. Diet Composition

	Control	High Protein	Low Protein
kcal/100 g (calculated)	341	412	412
Composition %			
Protein	26.5	55.0	3.5
Carbohydrate	43.0	30.0	81.5
Fat	7.0	8.0	8.0
Other*	23.5	7.0	7.0
	100.0%	100.0%	100.0%

*Minerals, vitamins, fiber, and moisture

diets. The high and low protein test diets (HP and LP)* were prepared according to the Hegsted and Chang method.¹³ The variation in protein content was compensated for by a proportionate change in carbohydrate content which yielded equal caloric values for both test diets. In order to pellet the HP and LP diets the carbohydrate was provided as cornstarch (15%) and sucrose. All three diets contained vitamin supplements and the animals were allowed *ad lib.* access to their respective diets.

Pilot Studies

In order to provide rats with similar body weights at the time of experimental hemorrhage, a pilot study was conducted to determine the time required for rats on each diet to reach a given range of body weight. Rats were weighed every 3 days and those on HP and C diets gained steadily from their initial weight while the rats on LP diet lost weight for 7 to 10 days but subsequently maintained a constant weight for at least 3 weeks.

From this preliminary study it was determined that large rats (350-375 g) should be fed LP diets to reach a final weight of about 340 g by the time of the shock study and that small rats (initially 225 g) should be fed HP and C diets in order to reach a similar final weight within the same time span (3.5 to 7 weeks).

*Obtained from General Biochemicals, Laboratory Park, Chagrin Falls, Ohio.

Since growth curves are not linear with time, a pilot study was made to compare the growth curves of 7 rats, from both the HP and C diet groups, which started with identical weights (Fig. 1).

Four rats were maintained on the LP diet for 9 weeks to determine the stability of body weight with prolonged consumption of this experimental diet (Fig. 1).

Shock Models

Six hours before hemorrhage, food was removed from the rat's cage. Anesthesia was administered 90 minutes preceding hemorrhage by an intraperitoneal injection of Nembutal (5 mg/100 g body weight). Tracheal intubation was not performed. The rectal temperature was maintained within the range of 37-39 C by the intermittent external application of heat. One common iliac artery was cannulated and connected to a mercury manometer; the contralateral artery was cannulated and connected to a reservoir. Each cannula included a stopcock for removing blood samples. One hundred units of heparin per 100 g of body weight was given intravenously and the cannulae were filled with a solution of heparin in saline (1000 u/ml) following withdrawal at each blood sample. Thirty minutes before hemorrhage and again immediately prior to hemorrhage blood samples were taken to obtain pre-shock values of hematocrit, pH, P_{CO_2} , and P_{O_2} , and blood glucose. Determination of hematocrit was made in duplicate by the micromethod; of pH, P_{CO_2} , and P_{O_2} with a Radiometer Blood Gas Analyser*; and of glucose levels by Boehringer Mannheim glucose oxidase assay.**

Hypovolemic shock was produced by two methods—Model I: hemorrhage to a pre-determined mean arterial blood pressure (MABP) (modified Wiggers model) and Model II: hemorrhage to a pre-determined volume of blood based on percent of body weight. In both models blood samples were taken at 30 minute intervals for analyses.

In Model I, 13 rats fed HP diet and 16 rats fed LP diet

*The London Company, Cleveland, Ohio.

**Boehringer Mannheim Corp., New York, New York.

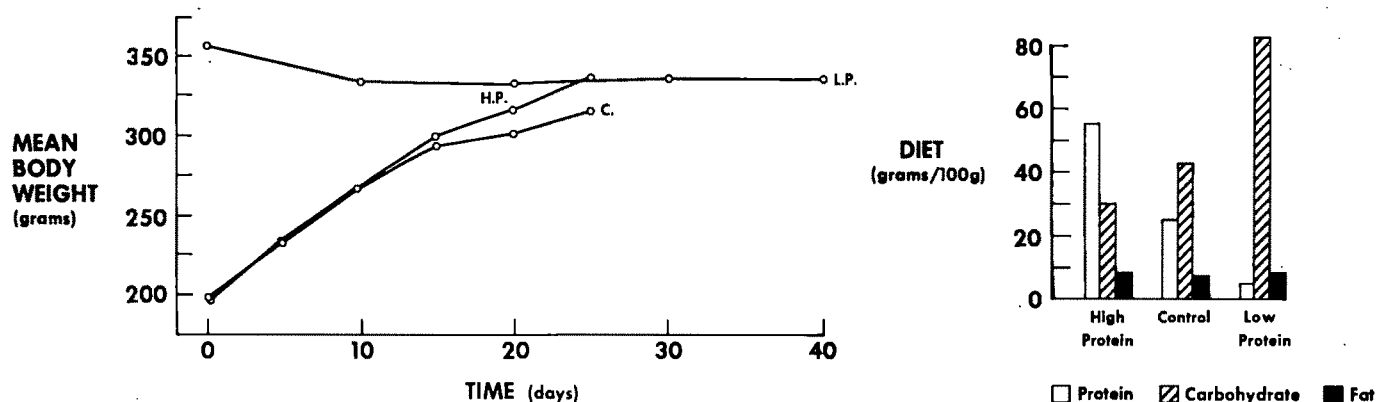


FIG. 1 Effect of dietary protein/carbohydrate on growth. LP—low protein; HP—high protein; C—control diet.

TABLE 2. Pre-shock Values

	High Protein n = 20	Control n = 22	Low Protein n = 19
MABP (mm Hg)	85.6±15.0	82.0±17.7	54.8±7.4
hct	49.0±1.9	47.6±2.2	41.5±3.1
blood glucose mg/100	141.0±12.9	130.6±12.2	139.6±13.2
pH	7.390±.024	7.420±.040	7.407±.023
P _{O₂}	80.3±6.3	79.3±10.0	80.1±6.2
P _{CO₂}	38.1±4.0	34.4±3.5	32.5±4.6

*± values = standard error

were subjected to hemorrhage to 40 mm Hg in 10 minutes. This MABP was then maintained by further bleeding or infusion (modified Wiggers model).⁵ The volume of blood removed to maintain the MABP was recorded every 5 minutes. Survival time was calculated from the beginning of hemorrhage until death.

In Model II, 20 rats fed HP diet, 19 rats fed LP diet, and 22 rats fed C diet were initially bled a volume equal to 0.8% of body weight which was the average volume of blood lost to reach a MABP of 40 mm Hg in a preliminary group of control rats. At 30 minute intervals thereafter until death, a volume equal to 0.5% body weight was bled as an approximation of the continuing blood loss necessary to maintain a reduced MABP of 40 mm Hg by the Wiggers model. Ten minutes were allowed for each episode of bleeding with a 20 minute recovery period. The MABP was recorded every 5 minutes. Every 30 minutes blood samples were taken for hematocrit, pH, P_{CO₂}, P_{O₂}, and glucose determinations. Survival time was calculated from the beginning of the first hemorrhage until death.

Results

The effect of diet on the physiological and metabolic parameters listed in Table 2 was recorded as typical baseline data for rats subsequently subjected to hypovolemic shock. The preshock values for pH, P_{CO₂}, and P_{O₂} were similar in all rats regardless of diet. However, the MABP and hematocrit were significantly lower in rats fed a LP diet compared with those fed either a HP or C diet ($P<0.001$).

For Model I, rats subjected to hemorrhagic shock by the modified Wiggers method, the mean volume of blood loss required to maintain a MABP of 40 mm Hg is illustrated in Fig. 2. The P values indicate a significant difference between the rats on HP and LP diets at each sampling time. The mean survival times for rats fed a HP diet or a LP diet is recorded in Table 3. The hyperglycemic response was greater in animals fed a HP diet than in those fed a LP diet (Fig. 3). In rats fed a LP diet the level

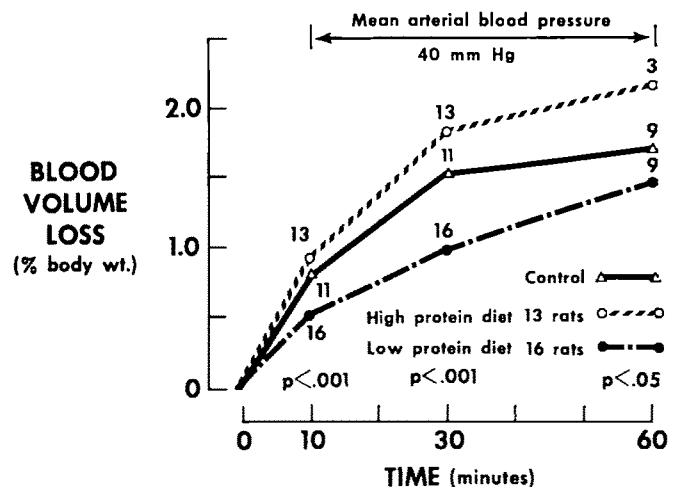


FIG. 2. Effect of diet on blood volume loss during shock. The P values compare the volume loss for rats fed HP and LP diets at each sampling time.

of blood glucose had declined by the time of death of the animals to hypoglycemic levels, 26 mg/100 ml below the preshock value.

When rats were bled on the basis of body weight (Model II), all animals regardless of diet demonstrated good initial recovery of MABP, almost to preshock

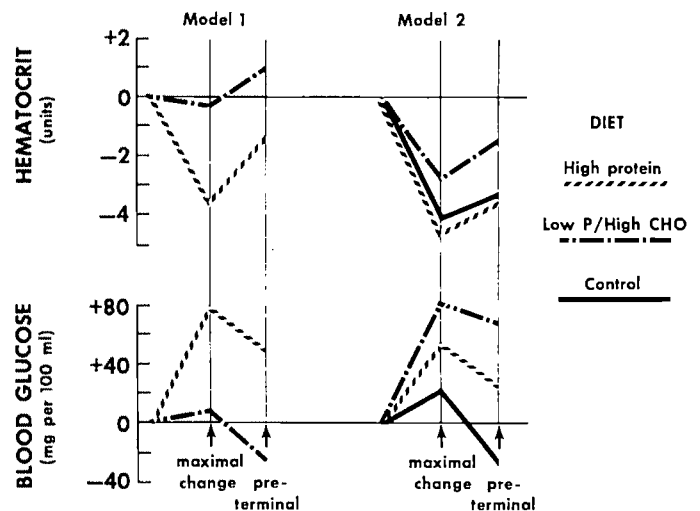


FIG. 3. Effect of diet on changes in hematocrit and blood glucose during shock. Significance (two-tailed *t* test): For the maximum change in hematocrit values in: Model I high protein vs. low protein $P<0.001$. Model II control vs. low protein $0.05<P<0.10$; high protein vs. low protein $0.01<P<0.02$; high protein vs. control $0.6<P<0.7$. For the maximum recovery in pre-terminal hematocrit values in Model I high protein vs. low protein $0.10<P<0.20$. Model II high protein vs. control $0.80<P<0.90$; control vs. low protein $0.05<P<0.10$; high protein vs. low protein $0.025<P<0.05$. For the maximum change in blood glucose values in Model I high protein vs. low protein $0.02<P<0.025$. Model II high protein vs. control $0.001<P<0.005$; control vs. low protein $P<0.001$; high protein vs. low protein $0.10<P<0.20$. For maximum fall in pre-terminal glucose levels in Model I low protein vs. high protein $0.025<P<0.05$. Model II high protein vs. control $P<0.001$; control vs. low protein $P<0.001$; high protein vs. low protein $0.025<P<0.05$.

TABLE 3. *Survival Time*

Diet	Survival Time	
	Model I	Model II
High Protein	55.1±13.4 min	99.3±15.0 min*
Control		95.2±18.0 min
Low Protein	67.1±20.8 min	82.4±22.4 min

*± values = standard error

Significance (two-tailed t test):

Model I: High protein vs. low protein = $0.05 < P < 0.10$

Model II: High protein vs. control = $0.40 < P < 0.50$; High protein vs. low protein = $0.005 < P < 0.01$; Control vs. low protein = $0.025 < P < 0.05$

levels. However, survival after the third bleeding episode was reduced in animals fed a LP diet compared with that of rats fed HP or C diets. Total survival times from the first hemorrhage until death are recorded in Table 3.

In contrast to Model I animals, rats fed a LP diet and subjected to shock by hemorrhage to a pre-determined volume (Model II) exhibited a greater hyperglycemic response than did rats fed HP or C diets. In addition, the blood glucose level remained elevated and was significantly higher in the pre-terminal sample in the rats fed a LP diet. While the blood glucose concentration of the rats fed HP diet was lower than that of the rats fed LP diet, it was higher than rats fed C diet (Fig. 3).

Fig. 3 also illustrates that during shock the hematocrit fell the least in animals fed a LP diet regardless of the shock model employed.

There was a progressive fall in pH throughout the course of shock produced by either model, associated with a fall in P_{CO_2} and a rise in arterial P_{O_2} . No significant difference in these values was observed among the rats regardless of diet or shock model employed.

Discussion

The results of this study indicate that a low protein/high carbohydrate diet will significantly impair the homeostatic capacity of rats to withstand repeated episodes of blood loss. The following discussion will eliminate several possible causes for this effect in each shock model and explain why the most likely cause is altered carbohydrate metabolism.

Diet and Stress

It is unlikely that chronic caloric depletion exerted a significant influence in this study since the animals fed the low protein/high carbohydrate diet maintained a stable body weight for 3.5 to 7 weeks. The initial weight loss was only 6% of the mean starting weight; however, the low protein content of the diet undoubtedly had a critical effect on total body metabolism as reflected in the hypotension and anemia (Table 1) recorded in these animals prior to hemorrhage.^{17,20}

The significant decrease in survival time for animals fed a LP diet when subjected to recurrent hemorrhage (Model II) is consistent with an extensive literature indicating the detrimental influence of protein depletion on tolerance to stress.^{8,18,19} Frequently, however, the low protein intake is associated with low caloric intake so that it is difficult to ascertain whether the impaired tolerance to stress reflects only protein deficiency or both protein and caloric deficiency. In this study care was taken to provide caloric intake adequate to maintain body weight (Table 1).

In contrast to the results of Elman⁷ with dogs subjected to shock similar to Model II, in this study those animals fed a HP diet did not exhibit a longer survival time than rats fed a control (C) diet (Table 3). The greater rate of weight gain in rats fed HP diets than rats fed C diets does, however, suggest a significant influence of the diet on body metabolism (Fig. 1). The fact that HP and C rats were selected for study at a time when their body weights were within a similar range may have obviated an intrinsic benefit of a high protein intake suggested by the greater rate of weight gain in those rats fed a HP diet. It is interesting that some studies indicate that a HP diet may actually exert a detrimental influence after stress.⁴ No such effect was apparent using Model II in this study; rather, the animals fed a HP diet responded as well or better than those on C diets and significantly better than animals fed a LP diet (Table 3).

Hypotension

The hypotension found in the rats fed a LP diet may reflect a decrease in blood volume.¹⁷ The severe hypotension in turn was probably responsible for the small volume of blood loss required to reduce the pre-shock mean arterial blood pressure from 54 mm Hg to the pre-determined arbitrarily selected level of 40 mm Hg upon hemorrhage by the modified Wiggers model (Model I) (Fig. 2). In contrast, a significantly greater volume loss, indicative of a higher preshock MABP and a more effective homeostatic mechanism, is required to achieve and maintain the low level of blood pressure of 40 mm Hg in the rats fed the HP diet than is required in those fed the LP diet.

In view of the marked differences in blood loss between rats fed HP and LP diets in Model I, it is not surprising that the mean survival time for the protein-deficient rats was longer than for the rats fed a HP diet. But the blood volume loss was so consistently and significantly greater for rats fed a HP diet that it was necessary to employ a different shock model for another comparison of survival times (Model II).

In Model II it is unlikely that a reduced blood volume was entirely responsible for the decreased tolerance to shock in the rats fed a LP diet since reduction in blood

volume with protein deficiency is proportional to reduction in body weight¹⁷ and the animals in this study were bled on the basis of their body weight. The recovery of MABP of all animals after their initial hemorrhage regardless of diet was particularly surprising for those deficient in protein in view of their low pre-shock MABP. This suggests that factors in addition to blood volume and cardiovascular performance are involved in decreased tolerance to repeated blood loss. There is an increased workload placed on the cardiovascular system by a reduction in red blood cell mass, but the reduction in hematocrit must be marked before a significant influence on tolerance to acute hemorrhagic shock is evidenced.⁵

It is probable that low protein diet results in a reduction of plasma oncotic pressure through inadequate protein synthesis.²¹ Such reduction in oncotic pressure would account for the significantly impaired refill of plasma from interstitial spaces during hypovolemia as evidenced by the lesser fall in hematocrit with either shock model ($0.001 < P < 0.025$) for rats fed the LP diet. While the blood loss in the modified Wiggers model (Model I) may have been insufficient to induce a drop in hematocrit, the blood volume removed on a basis of body weight (Model II) was certainly adequate, as evidenced by the marked fall in hematocrit that occurred with this model, for rats fed HP and C diets (Fig. 3). It is now recognized that capillary-interstitial fluid exchange during shock is a more complex process than the Starling-Bayliss hypothesis and depends, probably to a considerable extent, on energy use.¹⁵

Carbohydrate Metabolism

The hyperglycemia that occurs during shock (Model II) might be expected to exert an osmotic effect, pulling interstitial fluid into the circulation. That it did not do so in the LP rats, indicates the severity of impairment of the mechanism responsible for refill of plasma from interstitial fluid. Failure to observe a significant hyperglycemic response in LP rats in Model I probably reflects the small blood loss in these animals since rats fed an identical diet manifested a marked rise of blood glucose level when subjected to a greater blood loss (Model II).

The striking finding in this study is the magnitude of the hyperglycemic response to shock in the LP rats in Model II with the high level of blood glucose persisting during the terminal phase of shock in these animals. A high carbohydrate intake is known to expand the hepatic stores of glycogen.^{2,20} Due to the action of epinephrine, liberated as an integral part of the homeostatic response to hypovolemic shock, there is rapid catabolism of the large hepatic glycogen stores. This could account for the greater rise of blood glucose level than that found in the C or HP rats during the early phase of shock. Ordinarily, however, the level of blood glucose declines progressively with continuing shock and this fall in blood glucose

level correlates with the onset of physiological deterioration (5,19). In fact, some degree of prolonged tolerance to persisting shock can be achieved by the infusion of a bolus of glucose at the time homeostatic mechanisms begin to fail.¹⁶ The fall in blood glucose level after the initial hyperglycemic response has been ascribed to depletion of hepatic glycogen while the peripheral tissues continue to take up glucose.³ In dogs peripheral uptake is accelerated during shock and the increased rate of removal of glucose from the blood occurs so long as hypovolemia persists.⁶ Presumably, the need of hypoxic cells for additional glucose to support their energy metabolism is sufficient to overcome the inhibition of cellular uptake expected in view of the high blood levels of epinephrine and cortisol. The role of insulin, however, as a determinant of peripheral uptake of glucose during shock remains to be clarified.

The high level of blood glucose observed at the time of death in rats fed a high carbohydrate/low protein diet might reflect hepatic output of glucose from the large stores of glycogen which continues to exceed peripheral uptake. But previous studies suggest that tolerance for hypovolemia persists until hepatic glycogen is depleted and the level of blood glucose declines.^{16,19} While many factors undoubtedly contribute to loss of tolerance to shock our hypothesis is that a key requirement for homeostasis is the continued supply of energy. If this is true it would be difficult to explain the significantly decreased survival time of the LP rats when their pre-terminal level of blood glucose was significantly higher compared with rats fed C and HP diets.

Several studies of kwashiorkor suggest a possible interpretation of the paradoxical finding of hyperglycemia in the pre-terminal blood samples in Model II (starvation in the midst of plenty). Using labeled glucose, Gillman demonstrated a decreased rate of removal of blood glucose in the presence of dietary protein insufficiency and a high carbohydrate intake in humans.⁹ Many studies indicate a deficiency of insulin effect but it has not been clearly established whether the impairment relates to insulin synthesis, release, or peripheral action.^{1,2,12,14} Whatever the precise mechanism may be, the consensus is that a low protein/high carbohydrate diet impairs peripheral uptake of glucose.^{1,2,11,12} Undoubtedly, some uptake occurs and this is reflected in the results of studies with Model I in which the blood glucose levels fell to hypoglycemic levels during shock. But in this model, the blood loss may have been too small to stimulate an appreciable release of hepatic glycogen. Clearly, studies of hepatic output and peripheral uptake of glucose during shock are necessary to account for the terminal hyperglycemia.

Thus the hypothesis is advanced that although an abundant supply of blood glucose is available as an energy source during shock, uptake of glucose by

peripheral tissues is inhibited and thus homeostasis is curtailed in animals maintained on an antecedent high carbohydrate diet with a low protein content. While the mechanisms involved and the hypothesis itself require further study, the results indicate that some minimum amount of protein is required for adequate carbohydrate metabolism. This requirement becomes particularly obvious under the conditions of stress such as hemorrhagic shock when energy use is apparently increased.

Acknowledgment

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DISCUSSION

DR. STANLEY DUDRICK (Houston, Texas): About three or four decades ago in the Harrison Department of Surgical Research at the University of Pennsylvania, Drs. Ravdin, Parkins, Vars and Rhoads were interested in studying the effect of hypoproteinemia and its associated decreased tolerance to shock both in dogs that were plasmapheresed and in rates that were hypoalbuminemic after having been fed protein-free diets for several weeks. I recall they tried to correlate primarily the degree of hypoproteinemia with the rapidity with which the animal might go into hypovolemic shock, and these were among the earlier such studies that Dr. Drucker mentioned, together with those of Elman and many other teams throughout the country at that time.

Dr. Drucker has described a phenomenon here that I think perhaps even he didn't expect exactly, the fact that his animals did maintain the same weight while he was feeding some of them isocalorically high carbohydrate, low protein, rather than high protein low carbohydrate, certainly bespeaks some subtle change in the body composition of these animals. I suspect that there was probably a decrease in total body protein, and an increase on body fat and water.

It would be interesting—and he may already have these data to some extent—to know what the body composition of these animals might be, not only in the serum, but also in the tissue. I'm sure there's some protein-related mechanism that allows a vast difference in the degree response to injury. You probably have all experienced, in the immediate posttrauma period, the tremendous difficulty in maintaining serum albumin concentration and normal oncotic pressure, despite the fact that large amounts—perhaps 150 gm of albumin per day, and

perhaps another 150 gm of amino acids—are given by vein in various forms of total intravenous therapy.

So something happens, particularly under conditions of shock and trauma, that interferes greatly with protein metabolism. I hope that his work and others' might some time elucidate some of the mechanisms.

Dr. Drucker, I was wondering if you have any means by which you can determine how much of the rise and persistence of the hyperglycemia might be due just to the increased carbohydrate load, and how much might be due to some form of impaired glucose metabolism.

Also, I was wondering if you did do any serum albumin measurements, and whether you might have actually studied the liver itself histologically, or histochemically, to determine or to correlate any change in the animal, together with the increased susceptibility to shock, particularly in your low-protein, high-carbohydrate animals.

DR. JONATHAN E. RHOADS (Philadelphia, Pennsylvania): I rise to congratulate Drs. Drucker, McCoy and Howard on what I think is a very elegant study. The study that Dr. Stanley Dudrick referred to that we did was quite a crude study. We were anxious to get an effect, so we did plasmapheresis on dogs, and kept them on an almost protein-free diet until their proteins came down about to edema levels. We then put them through a shock procedure which was similar to the second one that Dr. Drucker described. When we had bled them enough times so that their blood pressure stayed under 60 mm Hg for 30 minutes, we considered this the end point.

On that basis, the normal animals required an average loss of 4.5% of

body weight, and the hypoproteinemic animals only 2.7%. We had five or six animals in each series, and there was no crossover of the figures at all.

Dr. George Whipple showed the body is something of a sponge for protein. He referred to the mobilizable protein as labile protein, and pointed out that this could vary in amount, and that if the animal was disadvantaged by diet, this would be reduced. He measured it by doing plasmapheresis, until the dog's N output came down to a steady level (the dietary intake being controlled) and then he subtracted the extra nitrogen which was excreted in the urine in the first few weeks—from the average level attained when the N excretion became constant.

The labile protein is, I think, an important factor that must vary greatly and these experiments would seem to show that it can vary on the down side. In part, at least, the results could be explained in this way—that the animal on the poor protein diet could mobilize very much less labile protein.

One can question whether animals can mobilize very much of this protein in the half-hour to hour of these experiments, but I believe they can mobilize an appreciable amount.

Dr. C. Everett Koop did some experiments in the opposite direction, hyperalimentering patients with a gastric tube or by mouth giving them something of the order of 8000 calories, and about the equivalent of 300 gm of protein a day. He studied patients admitted often for brain surgery, who had no specific weight loss or had bad dietary history, and to my very great surprise he was able to put them so far into positive nitrogen balance in five days that this would exceed the amount of the negative nitrogen balance in the five days after a major surgical procedure.

The experiments reported by Dr. Drucker and his associates are elegant in the way they are conceived, and elegant in the results obtained, and I again want to congratulate the authors.

PROFESSOR J. PHILIP SANDBLOM (Lausanne, Switzerland): When one has heard a beautiful paper like this on experimental subjects, one always speculates on the relationship with clinical work.

After we had some years of experience with wound healing problems experimentally, we were eager to see what relevance it has for clinical care, so we developed a method by which we could, not experiment, but examine the tensile strength of healing wounds in patients.

The factor which influenced wound healing the most, and really depressed it with statistical significance, was Cushing's disease, but next to that came old age, followed by hypoproteinemia. Here hyperalimentation would have a great field, as has already been shown in enterocutaneous fistula.

DR. WILLIAM R. DRUCKER (Closing discussion): To reply to some of his comments—and I thank Dr. Dudrick and Jonathan Rhoads and

Philip Sandblom for discussing the paper—there is considerable data in the literature about the body composition of animals maintained on a low-protein diet. There is relatively scant data about the composition of animals on a low-protein but a very high-carbohydrate diet. However, there is some, and these data suggest that these livers are just chuck-full of carbohydrate in the form of glycogen, as well as chuck-full of lipid.

Now, there have been some electron microscopic studies endeavoring to try and find out whether these changes in the cellular structure, which I can't remember to describe for you—whether the cellular structure changes can be reversed: and I think most of the few studies that have been done suggest that they are reversible if the diet is improved. Of course, this is terribly important in the children with kwashiorkor, and it's important for our patients, if we have inadvertently kept them on a very high intake of dextrose infusion with minimal attention to their protein intake. That's where it was relevant to our clinical studies of this work.

Insofar as what happens to the blood volume, it goes down, and there are data from Murphy—this goes back to 1950—that show that it goes down in proportion to their body weight.

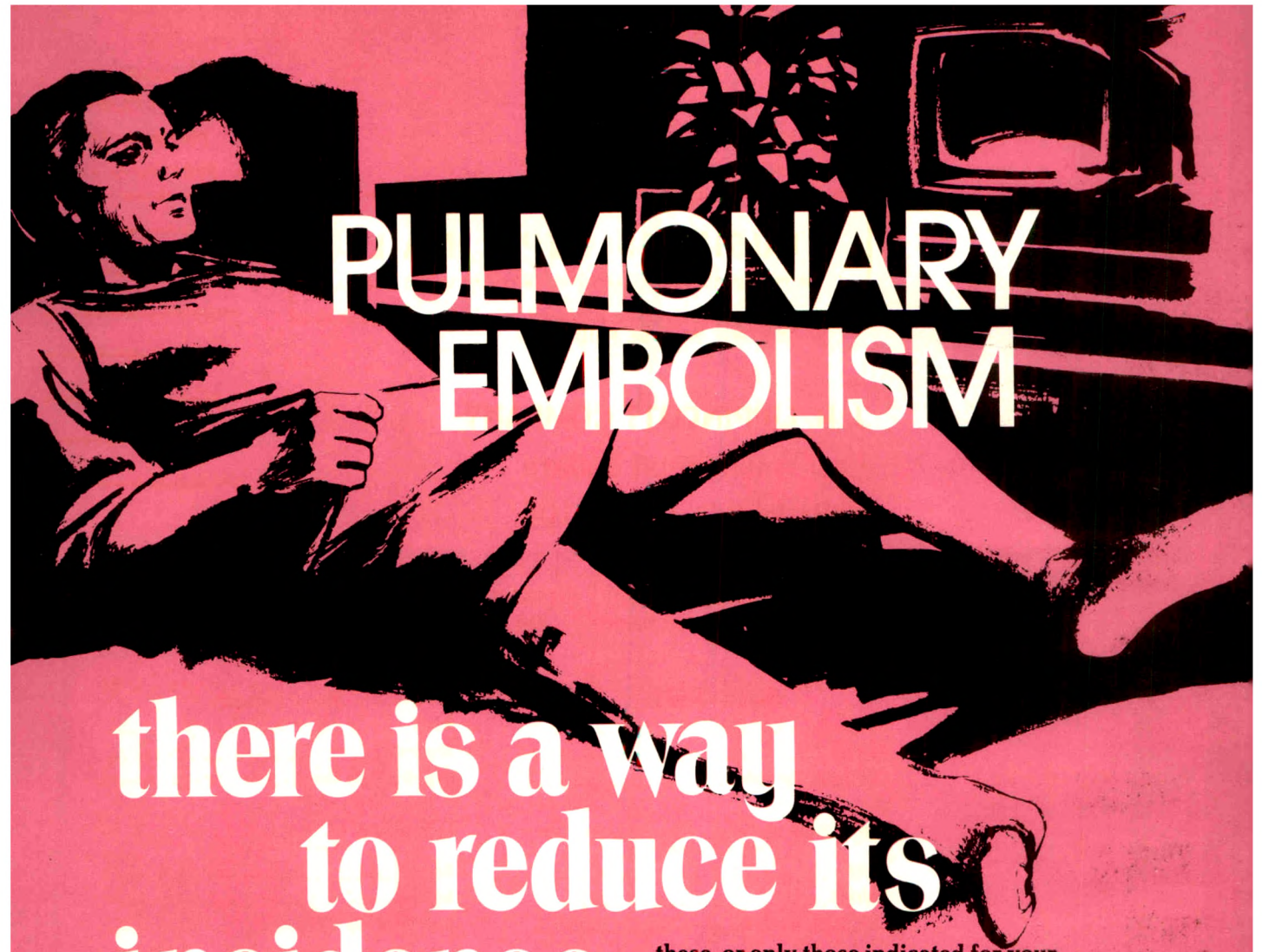
Now, there is a need to find out what happens in the experimental animal, because humans have a great edema, and we did not see edema under this circumstance in our rats. There's a lot of work that has to be done about the distribution of fluid, because of this impaired uptake that we found.

We didn't measure the albumin concentration. I think it would be surprising to find, however, that the albumin concentration of the blood is not low. I would expect it to be so.

One really must pay respect to the classical work that Jonathan Rhoads talked about that he did with Drs. Ravdin and Varis. There's another experiment they did which fits in beautifully, and this is their work on chloroform showing the liver would be much more tolerant if it has a glycogen supply; that one has to feed these animals to make sure that the liver has some glycogen in it, in order to make it resist poisoning of chloroform.

So we're caught somewhere in the middle. We want to give plenty of carbohydrate to protect that liver against all the toxic things we do in surgery, including shock. I mentioned that without glycogen the tolerance of shock is decreased; yet on the other hand we have to give enough protein to make sure that the carbohydrate that's present can be metabolized as well. I think the early studies of Jonathan Rhoads, Ravdin, and Varis show both ends of that spectrum. You've got to have carbohydrate, but watch out: You better have some protein as well.

I do appreciate the remarks of Philip Sandblom. There's no question that patients with a low protein intake develop impairment of wound healing. One question I would ask is: Is this simply due to the edema that's usually present, or is it due to the more basic defect that you don't have an energy supply to help with the wound healing?

A black and white photograph of a woman lying in a hospital bed, wearing TED stockings. She is looking towards the camera. The background shows a hospital room with a window and some plants.

PULMONARY EMBOLISM

there is a way
to reduce its
incidence.

Pulmonary embolism is considered one of the most common causes of post-operative mortality, a frequent occurrence in the medical patient and the greatest single cause of maternal deaths due to childbirth.¹ Mortality figures of 50,000 to 150,000 are cited. 95% of pulmonary emboli originate as thrombi in the leg veins and pelvis.²

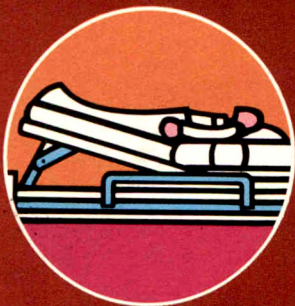
What causes the initial thrombus is open to debate. We know that venous stasis, changes in blood coagulability and vessel damage all may play a part, but which one—and how much?

Pulmonary embolism can be reduced through a rigidly implemented prophylactic program. The five basic elements are bed elevation, passive and active exercise, elastic compression, ambulation and anti-coagulants. All of

these, or only those indicated for your patient, will lessen the danger of clot formation in the venous system.

Compression, by properly fitted elastic stockings, is a critical element in the program. When applied, compression acts on the deep veins of the legs where 90% of thrombi form. In 1973, Sigel et al documented that the velocity of blood in the femoral vein is increased when compression is applied.³ It has been demonstrated that the blood velocity increase is maintained.⁴ The conclusion made from the studies is that stasis, a commonly accepted contributing factor, is substantially reduced. Compression does work.

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Incidence and Significance of Intraperitoneal Anaerobic Bacteria

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To amplify recent interest in anaerobic infections following abdominal disease, trauma, or surgery, 512 consecutive patients subjected to emergency celiotomy had both aerobic and anaerobic cultures taken of peritoneal fluid as well as all complicating wound and intra-abdominal infections. Average time between peritoneal entry or abscess drainage and specimen incubating under anaerobic conditions was less than two minutes. During 4 of the seven study months, patients had antibiotic therapy randomized, with clindamycin or cephalothin being sole parenteral agents and given intravenously prior to operation and for 5 days thereafter. Results demonstrated that anaerobes uniformly contaminate the peritoneal cavity whenever distal or obstructed intestine has been perforated, irrespective of the cause. Although all but one of the 123 complicating wound and intra-abdominal infections were due solely or at least in part to aerobic pathogens, $\frac{2}{3}$ of such infections also contained one or more different anaerobic species acting in synergism with the aerobes. No significant difference in incidence of postoperative infection or in infecting bacteria could be found with respect to antibiotic administered or etiology of perforation. Indeed, duration of bacterial exposure to atmospheric oxygen was the most critical factor influencing culture recoverability of anaerobic organisms, likelihood of ensuing wound or peritoneal sepsis participated in by an anaerobe, and success in control of established infections harboring anaerobes.

COINCIDENT with the introduction of clindamycin into the market of prescription available antibiotics, interest in anaerobic bacteria and their attendant infections has been suddenly rekindled and has steadily increased.¹⁸ Without doubt this new antibiotic is highly effective on *in vitro* testing against most species of anaerobes isolated from human infection and, in particular, *Bacteroides fragilis*.^{5,9,10} In addition, it is now certain that anaerobic microorganisms play a more significant role in surgical infections than previously had been appreciated and that, accordingly, antimicrobial therapy directed specifically against anaerobes is often warrant-

ed.^{1,2,4,7,12,13,15,17,18} Nevertheless, there is still a relative ignorance as to the frequency and importance of anaerobic bacterial participation in those septic states associated with intra-abdominal disease, trauma, and operation.^{7,14}

Since the thorough literature review by Altemeier in 1938 and his clear documentation that both anaerobic and aerobic species of bacteria are responsible for peritonitis in perforative appendicitis, few reports have referred to anaerobic microbes being involved in infections that develop after peritoneal, pelvic, or perineal contamination by intestinal contents.^{1,7} During the past four years, Gorbach and his associates have repeatedly stressed in several publications an almost routine soilage of the peritoneal cavity by anaerobes whenever gastrointestinal perforation has occurred because of disease or trauma.^{7,17,18} Infections that subsequently follow such contamination have also been due to a multiplicity of bacterial species having both anaerobic and aerobic culture requirements. Indeed, this synergistic combination of aerobes and anaerobes has appeared to represent to some investigators a valid argument to support the polymicrobial basis, rather than a single species cause, for the majority of infections relegated to the surgical ward.

Failure to deliver a proper specimen—promptly and under strict anaerobic conditions—to a bacteriology laboratory experienced and adequately equipped for anaerobe work has been the major reason for a lack of knowledge in this area.^{5,7-10,17,18} At present, however, most medical centers do have the capacity for reasonably accurate anaerobic bacteriology, and thus the culprit now responsible for a report of “no anaerobic growth” may well be the sampler, that is the surgeon, himself. Even a delay of only a few minutes in inoculation of the speci-

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ISOLATION OF ANAEROBIC BACTERIA

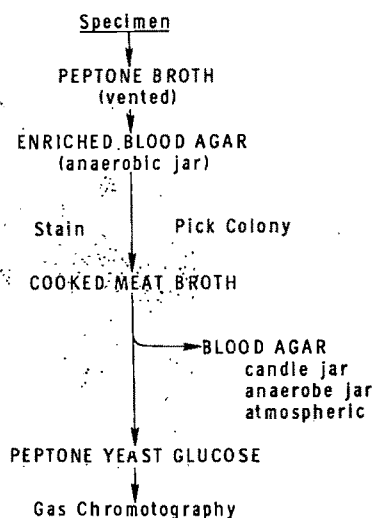


FIG. 1. Initial bacteriologic processing of anaerobic cultures.

men into an environment relatively devoid of oxygen can cause death of the very species of anaerobes that have invested a given infection with life-threatening virulence.

Clinical Study

During the seven month period from April 1 through October 31, 1973, all patients undergoing emergency celiotomy on the Trauma and Pediatric Surgical Services at Grady Memorial Hospital had anaerobic as well as aerobic cultures taken immediately upon peritoneal entry. The operating surgeon, after aspirating 1 or 2 ml of peritoneal fluid, then injected the specimen directly into a culture medium of supplemented peptone broth. A sterile venting unit was next inserted in order to allow for the escape of gases that would be generated by subsequent bacterial growth. Finally, the entire culture unit was then placed in a special incubator located within the operating

room suite and maintained at 37C. Although there were more perfected means available for culturing anaerobically, this particular method offered the important advantages of simplicity and practicality for individuals not skilled in such techniques as roll-tube inoculation. In addition, almost immediate incubation was assured.

Several of the patients had repeated peritoneal cultures taken at half hour or hourly intervals throughout the course of their operation, with some samples being obtained even as late as 4 hours after the abdomen had been opened. Identical methods were also used for culture of all complicating wound and intra-abdominal infections that developed postoperatively in these same patients, with the incubator in the operating room area again serving as the central collecting point.

Any patient exhibiting signs or symptoms suggestive of associated bacteremia had both aerobic and anaerobic blood cultures drawn. These were then processed just as expeditiously as were the more routine wound and peritoneal cultures.

Bacteriology

Within 24 hours of inoculation, tubes containing the broth cultures were picked up from the operating room and processed for both aerobic and anaerobic growth. Aerobic bacterial species were isolated and identified according to standard laboratory procedures, while testing for antibiotic sensitivity was carried out by the commonly employed disc technique of Bauer, et al.³

Apparent anaerobic isolates were first confirmed as being true anaerobes and only then were further identified (Fig. 1). Genus was determined by a few simple bacteriologic tests and gas chromatography (Fig. 2). Methods generally conformed to those described by Holdeman and Moore.⁶ Although speciation of all bacterial isolates was routinely done, it soon became obvious that, except for *Clostridia* and *Bacteroides fragilis*, de-

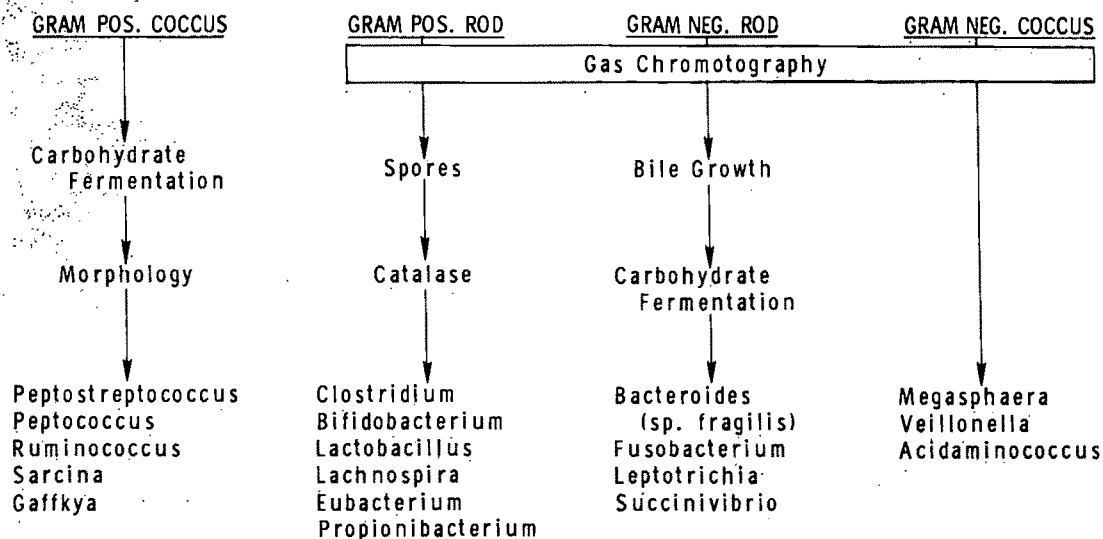


FIG. 2. Determination of the genus of anaerobic isolates.

	Patients	INCIDENCE OF INFECTION	
		Wound	Abdominal
Routine Cephalothin	202	26%	8%
Random Cephalothin	163	15%	3%
Random Clindamycin	147	14%	3%
TOTAL SERIES	512	19%	5%

TABLE 1. Incidence of postoperative wound and intra-abdominal infections.

termination of exact anaerobic species was of little practical value in routine clinical practice. Tests of susceptibility to clindamycin and to cephalothin were later run on all anaerobic isolates by means of a replicator and agar-dilution techniques.^{5,10}

Antibiotic Therapy

During the first 3 months, cephalothin was administered intravenously to all patients prior to, during, and for 5 days after operation. The usual dose was 2 gm given every 6 hours.

Randomization of intravenous antibiotics was then begun and continued throughout the last 4 months of the study. Patients with even hospital numbers received similar doses of cephalothin at the same intervals stated above. If, however the hospital number was odd, clindamycin was given intravenously on the same time schedule but at a dose of 300 mg. Evolution or worsening of sepsis seldom occurred prior to the fifth postoperative day; yet, when such did develop, an aminoglycoside (gentamicin or tobramycin) was added to the antibiotic regimen.

Tabulation

Results were analyzed on the basis of aerobic and/or anaerobic bacteria isolated, individual bacterial species, antibiotic sensitivity of these species, method of sampling, time of taking the specimen, source of the specimen, disease process accounting for the initial peritoneal contamination, incidence of later wound and peritoneal infection, species and frequency of complicating bacteremias, and antibiotic administered. Comparisons between initial peritoneal contaminants and bacteria responsible for subsequent infection were also drawn as were results and complications from use of the individual study antibiotics. Finally, an attempt was made to determine prevalence as well as importance of the anaerobic bacteria that so often contaminate the peritoneal cavity.

Results

During the 7 month study period, 512 patients underwent emergency celiotomy and provided the basic mate-

rial for culture analysis (Table 1). There were 202 patients in the first three months when cephalothin was the routine antibiotic. During the 4 months of randomization, an additional 163 received cephalothin; while 147 were given clindamycin. No significant differences could be found between types of cases or incidence of infectious complications with respect to the randomized patients given different antibiotics. However, the initial study group composed of consecutive patients receiving cephalothin had a greater incidence of both wound and intra-abdominal sepsis than did either of the randomized groups during the ensuing 4 months. This discrepancy could be explained only in part and then on the basis of greater attention to operative technique and wound care as well as by a significant reduction in frequency of colon injuries during the summer and early fall months.

Complications of antibiotic administration were common. Local phlebitis developed in 18% of patients receiving cephalothin, and this generally remained symptomatic for at least 5 days after cessation of the intravenous drip. Clindamycin, on the other hand, was associated with such a severe enteritis in 7% or so pronounced a rash in another 14% that the drug had to be discontinued. Thus the overall rate of adverse reactions to antibiotic therapy were not significantly different between the various study groups.

Aerobic Bacteria

Almost half, that is 244 of the 512 patients, had at least one species of aerobic bacteria contaminating their peritoneal cavity at the time of initial operation. This gave an incidence of 47.7%. There were a total of 460 aerobic isolates from the abdomens of these 244 patients, thereby giving an average of 1.89 aerobic species per patient and a range of one to five different species.

The most commonly grown organism was *E. coli*, representing more than a third of all of the aerobic isolates (Table 2). The total number of remaining gram-negative rods amounted to an even greater proportion, that is 43%. Of the gram-positive species, *Enterococcus* was the one most frequently isolated.

Antibiotic susceptibility of the aerobic bacterial isolates demonstrated a consistent superiority of the aminoglycosides, only a fair activity of cephalothin, and essentially no benefit from clindamycin except against species of *Staphylococcus* (Table 3). Only carbenicillin and, to some degree, gentamicin offered any reliability of action against the *Enterococcus*.

Anaerobic Bacteria

At least one species of anaerobic bacteria was recovered at initial culture from the peritoneal cavity of 159 patients, thereby producing an incidence of 31.1%. These 382 anaerobic isolates averaged 2.4 per patient, with a range of one to nine different species per patient.

GRAM NEGATIVE RODS

<i>E. coli</i>	164	35.7%
Kleb-Entero.	78	17.0
<i>Proteus</i>	69	15.0
<i>Ps. aeruginosa</i>	20	4.3
Miscellaneous	29	6.3

GRAM POSITIVE RODS

Miscellaneous	16	3.5%
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GRAM POSITIVE COCCI

<i>Enterococcus</i>	55	12.0%
<i>Staphylococcus</i>	13	2.8
(<i>sp. aureus</i>)	7	1.5)
<i>Streptococcus</i>	11	2.4

FUNGI

<i>Candida</i>	2	0.4%
Other	3	0.7

TABLE 2. Aerobic bacteria isolated on initial culture of the abdomen (460 isolates from 244 patients).

There was a great variation as to anaerobic genera, although *Bacteroides* was by far the largest group, representing more than 35% (Table 4). *Bacteroides fragilis* alone accounted for 14%. *Eubacteria* made up the next most frequently encountered genus, but this designation often became a catch-all term for unspecified gram-positive rods. *Clostridia* were noted in just over 7% of the total isolates.

Antimicrobial sensitivity testing was carried out for only two antibiotics—cephalothin and clindamycin (Table 5). The superiority of clindamycin was almost uniform and was most impressive against isolates of *Bacteroides fragilis*.

Incidence of Anaerobes

The pathologic and clinical progression of appendicitis from a simple erythematous process, through suppuration and gangrene, to its final stage of perforation was reflected in the incidence of aerobic and anaerobic cultures being positive (Fig. 3). Going from simple to suppurative appendicitis, there was a gradual increase in the frequency of aerobic species culturable from the peritoneal fluid. However, anaerobes were almost never present until gangrenous changes had developed in the appendiceal wall. On gross perforation, anaerobes became in fact the dominant microbial flora.

Other types of peritonitis had variable frequencies of anaerobic participation (Fig. 4). For example, perforation of a gastric ulcer led to much greater bacterial contamination by both aerobes and anaerobes than did the same event complicating a duodenal ulcer. Cholecystitis and pancreatitis were primarily chemical reactions during their earlier stages, while pelvic inflammatory disease was often due in part to anaerobic bacteria.

Following penetrating abdominal trauma, perforating wounds of the colon and rectum almost uniformly caused contamination of the peritoneal cavity by both anaerobic as well as aerobic species (Fig. 5). Perforations of the stomach and small bowel produced a soilage that paralleled what had been noted for rupture of gastric and duodenal ulcers. On the other hand, duodenal perforations due to trauma and the absence of any gastrointestinal injury rarely if ever led to noticeable bacterial contamination.

The spill of bacteria into the peritoneal cavity during surgery was another interesting feature (Fig. 6). If enterolysis without inadvertent enterotomy could be accomplished for the relief of mechanical intestinal obstruction, cultures had essentially no growth. However, the spill of obstructed small bowel contents produced a contamination that equalled what resulted when intestine was already gangrenous and required resection. In con-

ANTIBIOTIC AND DISC CONCENTRATION

	Number of Isolates	Gent. 10 mcg	Tobr. 10 mcg	Carb. 50 mcg	Ceph. 30 mcg	Chlor. 30 mcg	Kan. 30 mcg	Coly. 10 mcg	Clind. 2 mcg
<i>E. Coli</i>	164	99	99	89	65	95	81	96	0
Kleb-Enterobacter	78	100	100	27	41	95	86	91	0
<i>Proteus</i>	69	91	93	67	67	58	75	0	0
<i>Ps. aeruginosa</i>	20	95	95	80	0	0	0	100	0
Misc. Gram-neg. rods	29	97	97	79	52	90	83	93	0
<i>Staphylococcus</i>	13	100	92	85	100	—	—	—	100
<i>Enterococcus</i>	55	80	25	100	0	—	—	—	13

TABLE 3. Antibiotic sensitivity testing of initial aerobic bacterial isolates (Per cent of isolates sensitive).

TABLE 4. Anaerobic bacteria isolated on initial culture of the abdomen (382 isolates from 159 patients).

GRAM POSITIVE COCCI			GRAM NEGATIVE COCCI		
Peptostreptococcus	22	5.7%	Megasphaera	1	0.3%
Peptococcus	18	4.7	Veillonella	15	3.9
Ruminococcus	1	0.3	Acidaminococcus	4	1.0
Sarcina	1	0.3			
Gaffkya	1	0.3	GRAM NEGATIVE RODS		
GRAM POSITIVE RODS			Bacteroides	136	35.6%
Clostridium	29	7.6%	(sp. fragilis)	54	14.1
Bifidobacterium	11	2.9	Fusobacterium	13	3.4
Lactobacillus	10	2.6	Leptotrichia	9	2.4
Lachnospira	1	0.3	Succinivibrio	1	0.3
Eubacterium	75	19.6			
Propionibacterium	34	8.9			

trast, performance of a colostomy seldom necessitated opening the bowel until after the abdomen had been closed. Accordingly, this operation was associated with only a minor incidence of soilage, primarily due to aerobic species alone.

Exposure to Air

Prolonged exposure of the abdomen, a wound, or even an abscess cavity to air significantly reduced the chances of isolating an anaerobe. For example, in cases of perforative gastrointestinal trauma, the incidence of anaerobic bacteria being cultured from peritoneal fluid

diminished as the duration of exposure to atmospheric oxygen increased (Fig. 7). Although essentially all patients with colon wounds had initial contamination by anaerobes, such species of bacteria could be detected in only 10% one hour after the abdomen had been opened. Similar reductions in ability to detect the presence of anaerobes were noted in cases of gastric and small bowel perforation.

Even anaerobic bacteria actively participating in an established infection were susceptible to the adverse effects of atmospheric oxygen (Fig. 8). Although almost every specimen of peritoneal fluid from patients with

TABLE 5. Antibiotic sensitivity testing of initial anaerobic bacterial isolates.

ANAEROBE	NUMBER OF ISOLATES	ANTIBIOTIC TESTED mcg/ml	— PERCENT OF ANAEROBIC ISOLATES SENSITIVE —										
			<0.1	0.2	0.4	0.8	1.6	3.1	6.2	12.5	25	50	>50
Gram Positive Cocci	43	Clind. Ceph.	100 51	— 58	— 74	— 91	— 93	— 98	— 98	— 100	—	—	—
Clostridium	29	Clind. Ceph.	45 34	59 59	62 66	83 69	97 79	100 97	— 100	—	—	—	—
Eubacterium	75	Clind. Ceph.	57 43	79 57	85 60	89 65	96 65	99 77	100 84	— 89	— 100	—	—
Propionibacterium	34	Clind. Ceph.	100 29	— 79	— 88	— 97	— 100	—	—	—	—	—	—
Bacteroides fragilis	54	Clind. Ceph.	63 11	69 11	85 11	89 17	98 17	98 17	100 20	— 39	— 76	— 87	— 100
Bacteroides species	82	Clind. Ceph.	72 20	77 29	89 33	91 33	95 38	99 39	100 39	— 54	— 87	— 94	— 100
Other Anaerobes	137	Clind. Ceph.	45 30	61 40	65 46	81 74	94 80	98 93	98 97	98 100	100 —	— —	— —

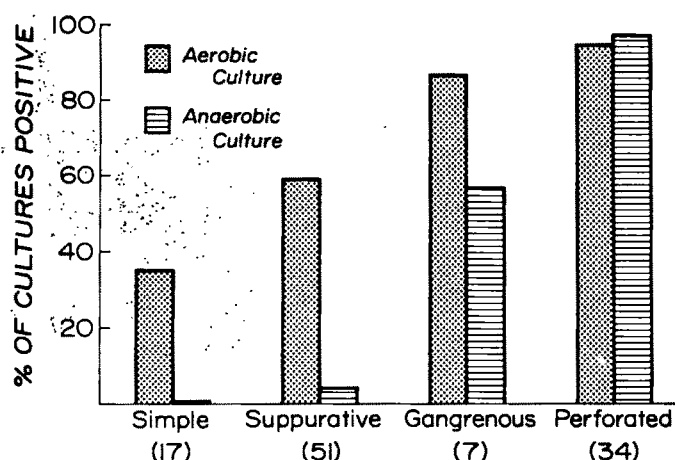


FIG. 3. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with appendicitis.

perforative appendicitis was positive for anaerobes if taken immediately upon surgical entry to the abdomen, this incidence fell to 30% by the end of one hour and to less than 10% after two hours.

A final example of the great sensitivity of anaerobic species to the adverse effect of oxygen in room air was noted when two different sampling methods were compared (Fig. 9). The recovery rate of anaerobes from specimens taken by a swab was only a fraction of what was obtained by aspiration and then immediate inoculation into an anaerobic medium.

Bacteriology of Infections

Irrespective as to the site of subsequent infection—be it wound or intra-abdominal—the frequency of anaerobe involvement was always significantly less than its relative population in the initial contaminant (Fig. 10). This reduction in incidence of participating anaerobes averaged 28%. It appeared that merely exposure of the wound or peritoneal cavity to atmospheric oxygen was the prime factor responsible for such a change.

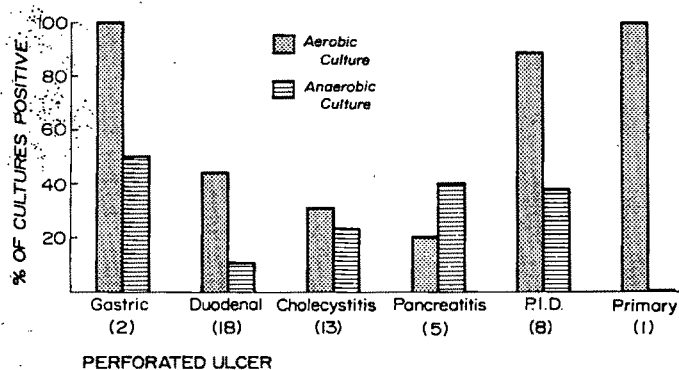


FIG. 4. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with various forms of peritonitis.

Complicating bacteremias developed in 21 patients (Table 6). Blood cultures yielded 69 different bacterial isolates, of which 21 or 30% were anaerobic species. In addition, it was noted that *Enterococcus* was more commonly grown from the blood than was *Bacteroides* with respect to both number of patients as well as total number of positive cultures.

No significant difference was found in frequency of aerobic or anaerobic bacterial participation in the post-operative wound and intra-abdominal infections when the two randomized treatment groups were compared (Fig. 11). This equality had not been created by case selection either, as both groups had similar proportions of aerobes and anaerobes contaminating the peritoneal cavity at the time of emergency celiotomy when initial cultures had been obtained. Likewise, there was no significant difference in the two groups of study patients, their diseases and injuries, associated medical conditions, or any other recognizable factor.

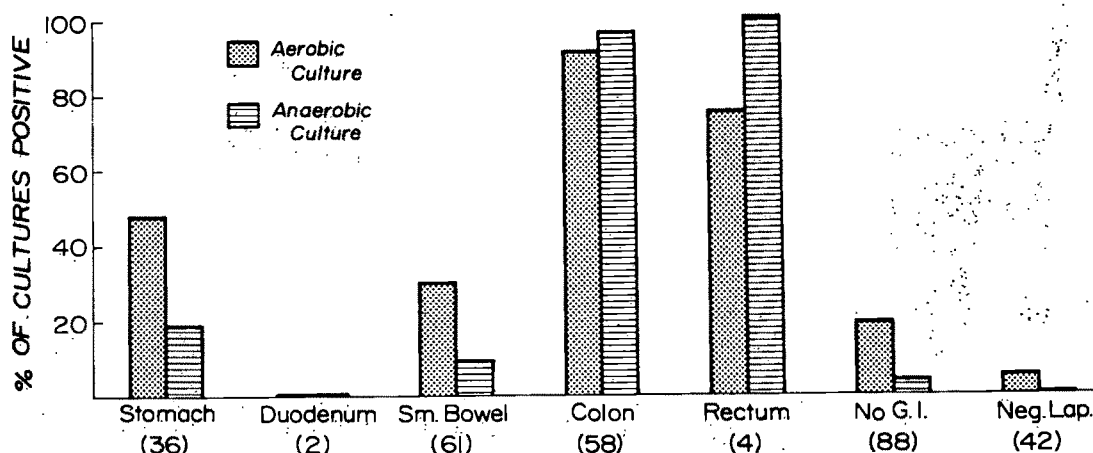
Discussion

Based upon previous reports as well as the present study, there appears to be irrefutable evidence that not only aerobic, but also anaerobic, bacteria uniformly contaminate the abdominal cavity whenever perforation of the colon or rectum has occurred.^{1,2,4,7,17,18} In addition, since the intraluminal flora of obstructed intestine parallels that of the large bowel, spill of such contents automatically soils the peritoneum with identical microbes. Subsequent wound and intraperitoneal infections in these patients likewise harbor anaerobic as well as aerobic species. Such has always been the case, even though unrecognized until recently. However, only dedication to proper culture technique and perfected methods for

	Patients	Cultures
Gram neg. rods	11	23
Enterococcus	7	13
Bacteroides	6	9
Eubacterium	4	6
Peptostreptococcus	4	4
Clostridium	2	2
Candida	1	3
Other	3	9
TOTALS	21	69

TABLE 6. Bacteria isolated from blood cultures in septic patients (Positive blood cultures in 21 patients).

FIG. 5. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with penetrating abdominal trauma.



anaerobe isolation and identification will permit these events to be more thoroughly appreciated.

Sampling Techniques

Anaerobes vary considerably in their susceptibility to the lethal effects of oxygen. Often the most virulent species contributing to a mixed infection dies before the specimen of pus can be properly inoculated and placed under strict anaerobic conditions. Thus, results of bacteriologic tests may well be false and fail to reflect the true microbial components of the infection. Accordingly, any sample to be processed for anaerobic growth should be taken quickly and with minimal contact to atmospheric oxygen. Aspiration of pus with a large bore needle and syringe is usually the easiest and most efficient method of sampling.

Next, the specimen must be inoculated into pre-reduced media and under anaerobic conditions as soon as possible.⁸ Anaerobic blood culture media, that is pre-reduced broths, are ideal. They require no expertise in roll-tube techniques or in any additional piece of equipment, such as the CO₂ pack or similar items. All neces-

sary media can be conveniently stocked in any hospital area, have a long shelf life, and are generally adaptable to any member of the health team for almost every clinical situation.

Finally, the specimen should be incubated immediately at 37°C. Otherwise, important species of anaerobes may be lost; for cold retards their cellular metabolism and thereby augments overgrowth by other and less virulent anaerobes.⁸

Requisites of Anaerobic Infection

Anaerobes can exist and propagate only when local oxidation-reduction potential has been significantly reduced. Such environments having a generally diminished oxygen tension are provided by necrotic tissue and marked local ischemia. These, despite being the more obvious and certainly the most classical manifestations of anaerobic infection, represent the extremes and account for only a small fraction of sepsis due to anaerobic species.¹⁵

By far the most common infections due, at least in part, to anaerobes are those that evolve as a synergism between aerobic and anaerobic bacteria. Growing in symbiosis, two or more different bacterial species with entirely opposite oxygen requirements may so alter the local environment by their metabolic end-products that conditions in the immediate vicinity become exceedingly conducive to survival and even rapid proliferation of the synergistic partners.^{11,12,15} Careful culture techniques by other investigators as well as methods used in the present study have consistently shown that the great majority of wound and intraabdominal infections complicating disease, trauma, or surgery of the gastrointestinal tract are based upon this symbiotic relationship.^{1,7,17,18} Indeed, strict anaerobe sepsis is rare, and even infections due solely to one or more aerobic gram-negative rods are probably uncommon under these conditions.

Some combinations of aerobic and anaerobic species have significantly greater virulence than do others, and thus the respective infections that they create likewise

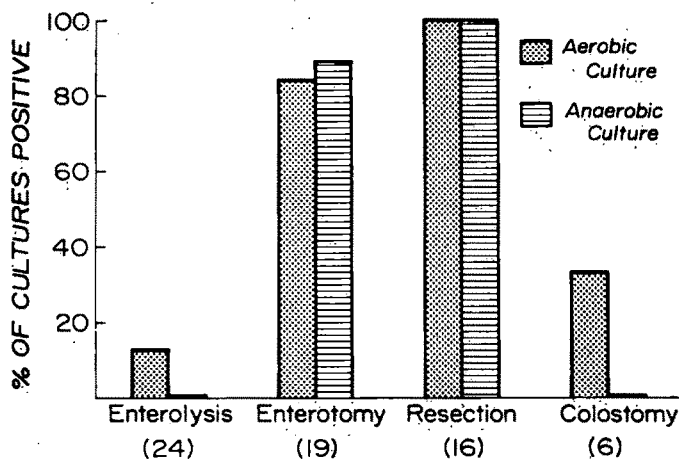


FIG. 6. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with intestinal obstruction.

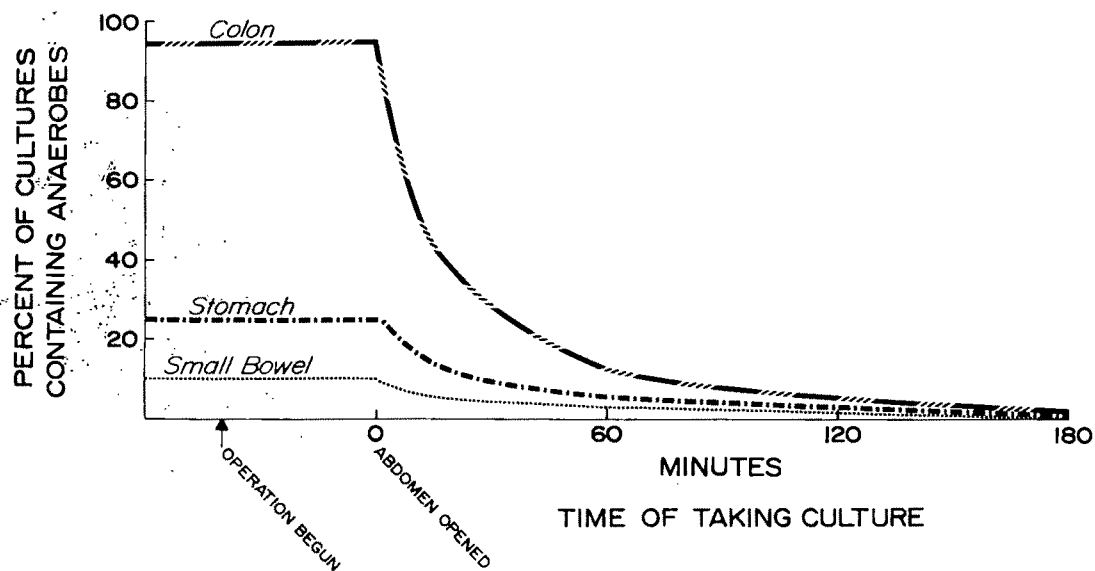


FIG. 7. Recoverability of anaerobes from the peritoneal cavity of patients with penetrating intestinal trauma.

vary in severity. However, the most critical factors determining patient susceptibility and progression of a given bacterial synergism are those associated diseases that limit host resistance. Diabetes mellitus, derangements in liver and kidney function, generalized occlusive vascular disease, extremes of age, obesity, and malnutrition appear to be the more detrimental of all precipitating diseases.^{2,4,7,12,13,15} Indeed, symbiotic infections in such individuals are so severe that specific names have been used to describe variations in anatomic location and responsible bacterial species.^{7,11,12,15}

Diagnosis of Anaerobic Infections

Since most anaerobic infections are in truth polymicrobial synergisms and since the majority encountered on any surgical service have evolved after disease, trauma, or surgery of the gastrointestinal tract, the basic clinical features are what have been described for many years as characteristics of gram-negative sepsis.^{7,14} However,

there are definite alterations in this pattern whenever anaerobic species contribute significantly to the sepsis. Fevers are higher and tend to spike; the patient is irrational; and jaundice may be present.¹⁵ Any one of these three additions should greatly increase suspicion that anaerobes are involved.

The wound itself has certain characteristics that are diagnostic. A putrid, often nauseating, odor is readily detected.^{7,15} Almost without exception, such unpleasant aromas are caused by gases produced only through anaerobic bacterial metabolism. In addition, the pus has a "dishwater" appearance because of a minimal number of leukocytes contained within.¹⁵ So-called "creamy" pus is packed with phagocytes, and only an active blood circulation locally can bring such corpuscular elements to the immediate area of infection. In contrast, gangrenous tissue or an environment replete with anaerobes characteristically has a poor vascular supply and thus a relative paucity of white blood cells.

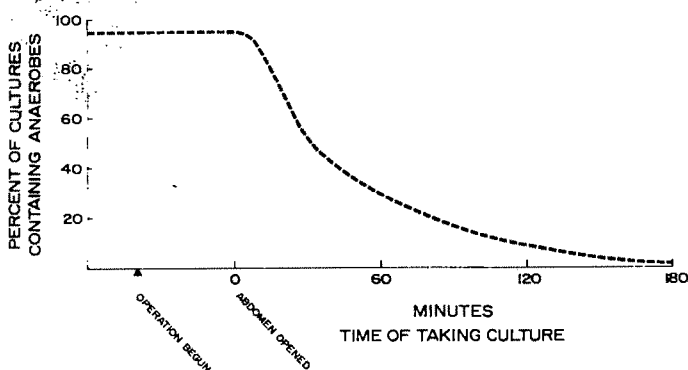


FIG. 8. Recoverability of anaerobes from the peritoneal cavity of patients with perforated appendicitis.

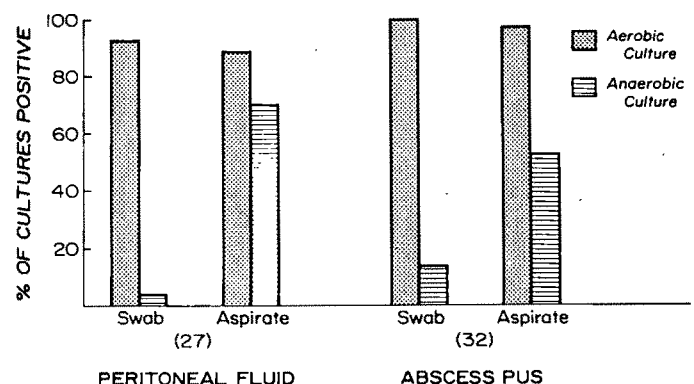


FIG. 9. Relative incidence of aerobic and anaerobic bacteria recoverable from the contaminated peritoneal cavity and from established infections of the wound or abdomen.

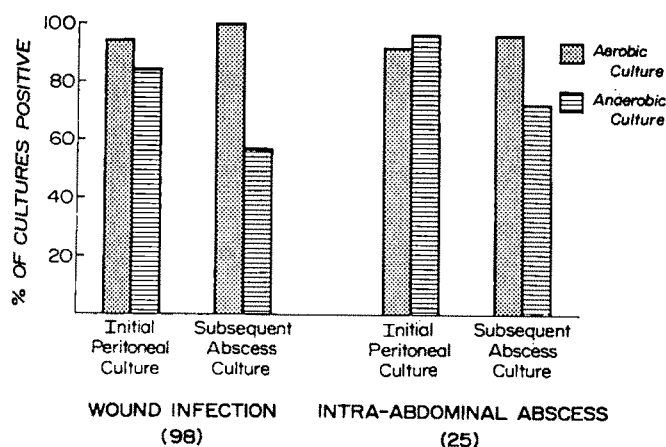


Fig. 10. Comparison of initial peritoneal cultures and subsequent infections in the same patients.

Principles of Treatment

Success in treatment of anaerobic infections revolves around two basic considerations: 1) alterations in local environment so as to impair or even kill the infecting anaerobes; and 2) administration of antimicrobial agents with specific activity against anaerobic species. There are many variations on these simple principles, yet all other measures of therapy are merely supportive unless based upon such tenets.

One way to change the local environment and thereby to preclude continued anaerobe survival is excision of all necrotic tissue and conversion of the infectious process to an open wound. Redox potentials are significantly increased by exposure to atmospheric concentrations of oxygen. Nevertheless, viable anaerobes may persist if aerobic species in the immediate vicinity can maintain a local, yet considerable, decrease in the oxidation-reduction potential. This dependency of anaerobic species on their aerobic counterpart probably explains the response, even though transient, of mixed infections in non-gangrenous tissues, such as the peritoneal cavity, to therapy with antibiotics active only against aerobic pathogens (Fig. 12). Elimination of the aerobic partner automatically increases the redox potential and thereby converts the area of infection to a hostile, oxygen-rich environment. Such may also explain the apparent equality of the two regimens of antibiotic therapy randomized in the present study.

An old colloquialism in surgery states that patients with peritonitis usually improve whenever "the abdomen had been opened to let sunshine in." This is in part a valid observation, and its application has benefitted many patients with peritonitis. However, the correction of anatomic defects; removal of purulent material, and, finally, direct exposure of abdominal parietes to atmospheric oxygen have undoubtedly produced the desired clinical improvement, not any beam of light.

Antibiotics Specific Against Anaerobes

Although *in vitro* tests have revealed that a number of presently available antibiotics are highly effective against most species of anaerobic bacteria, clinical or *in vivo* response is entirely dependent upon the antimicrobial reaching the actual sites of infection.¹⁴ Ischemic or frankly gangrenous tissues have been deprived of an adequate blood supply and therefore can essentially never acquire bactericidal concentrations of parenterally administered antibiotics. Thus, administration of an antibiotic active against anaerobic species can be of real value only: 1) in cases of bacterial synergism; that is when metabolism of the symbiotic aerobe has permitted infection by the anaerobe despite excellent circulation locally; and 2) in cases where an anaerobe bacteremia has complicated either a pure or mixed infection. It is only under these conditions that antibiotic can be delivered to infected tissues or a body cavity.

From a practical point of view, administration of antibiotics effective against anaerobic bacteria is always indicated if an anaerobic bacteremia has complicated the septic process. Such is almost certain to have occurred if no initial or lasting response is obtained by therapeutic doses of an aminoglycoside in cases of mixed infection or when one or more signs of anaerobic sepsis—high spiking fevers, irrational behavior, and jaundice—persist.

Probably the only other worthwhile reason to administer a specific parenteral antibiotic is when debridement or drainage of the infection must be delayed because of an as yet unrecognized source of infection, patient deterioration requiring energetic supportive measures prior to anesthesia, or some similar consideration. Although the patient may improve dramatically following such antibiotic therapy, recurrence of sepsis is an absolute certainty unless gangrenous tissues are debrided and the infection is converted to an open wound by either spontaneous or surgical drainage. There can be no substitute for this latter event; it is the mainstay of definitive therapy.

Of the several antibiotics with proven effectiveness

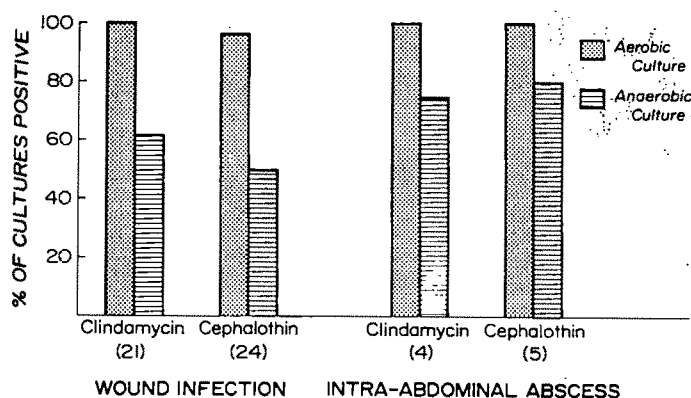


Fig. 11. Comparison of bacterial flora from patients receiving cephalothin and clindamycin.

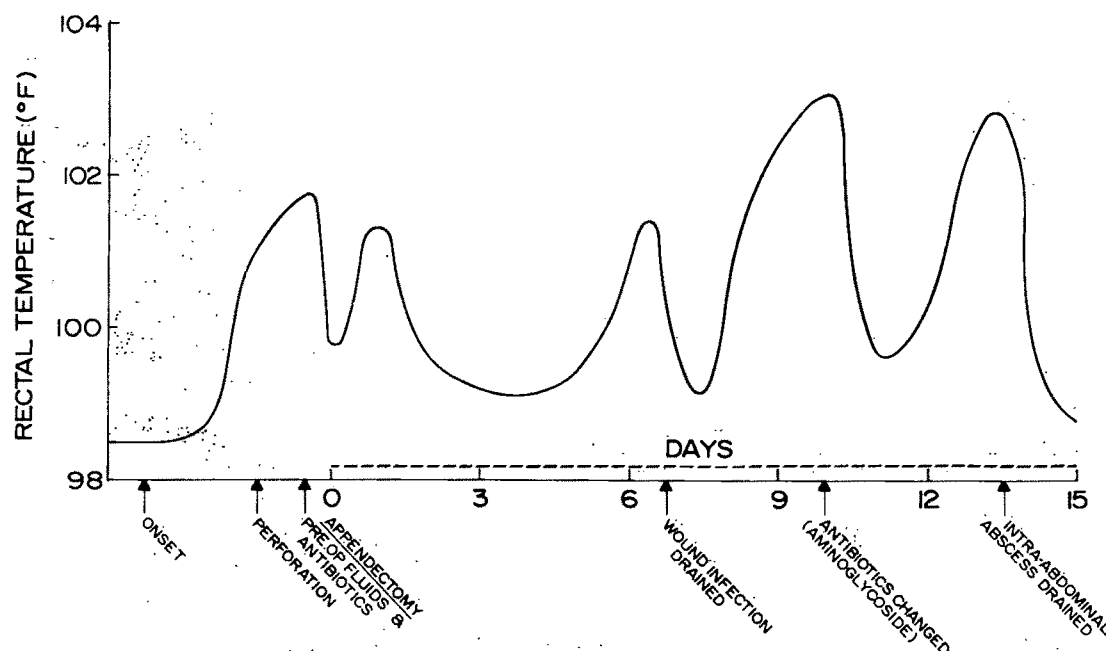


FIG. 12. Septic course of a patient treated for perforated appendicitis.

against anaerobes, erythromycin-related compounds appear at present to be the most reliable.^{2,4,5,7,9,10,13,17,18} Clindamycin certainly provides more certain coverage for all possible species, although erythromycin may well be its equal under clinical or specific laboratory conditions where tissue pH is within the physiologic range of 7.0 to 7.5.^{5,10} Other systemic antimicrobials that have been used in the past are chloramphenicol and tetracycline. Without doubt, chloramphenicol is the superior agent.

Unfortunately, use of clindamycin is associated with significant complications.^{6,7,16} Troublesome rashes are common, but the most dangerous of all its adverse reactions is the diarrhea that develops in approximately 20% of cases and the even more serious pseudomembranous colitis. This latter has been noted in almost 10% of all patients receiving a course of clindamycin, whether the antibiotic had been given parenterally or by mouth.¹⁶ Indeed, deaths have been documented as being directly attributable to this one complication.^{6,16} Thus, institution of clindamycin therapy should not be taken lightly and should be considered only if signs and symptoms indicate with considerable certainty that anaerobic bacteremia is present or an established anaerobic infection has as yet been poorly controlled.

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DISCUSSION

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): The paper Dr. Stone has presented, I think, will become the definitive work in this

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field, just as the work he shared with us on fungal sepsis in the surgical setting a year ago. I would make a couple of comments quickly: the quantitation that's been accomplished in Dr. Stone's study is extremely well done, and the value of the concurrent control, I think, in clinical

experiments is particularly well documented by the variable response rates he noted to the antibiotics, first in sequence, and then when run concurrently.

The second point I want to stress is that he again has pointed out that antibiotics are adjunctive methods of management to the definitive mechanical treatment of an infection, that is either to debride the necrotic tissue or to provide adequate drainage.

The only point with which I would disagree is a continuing emphasis against the long-term use of broad spectrum antibiotics. You will notice in his study he continued those drugs for five days. There's nothing magic about five days, and I think the sooner that we can terminate adjunctive therapy such as antibiotics in a patient who is responding appropriately from a clinical point of view, the less frequently that suprainfection will be a problem.

I would also draw your attention to that slide, which went by very rapidly, that reflects the three-hour appendectomy. I don't know whether this is standard at Emory, or just reflects my former chief's indisposition with his hand. I think that while it was, perhaps, not in keeping with optimum practice, it surely does provide excellent data on the effect of oxygen in destroying anaerobes in vivo.

Finally, I think the closing point about Dr. Stone's paper ought to concern the comment he made about anaerobic suicide. We have all listened for a year and a half or two years now to increasing suggestions that anaerobic bacteria are responsible for surgical sepsis, and they have been killing our patients for years, and we never knew it. Well, as a matter of fact, I think most experienced clinicians realized this was perhaps not quite the case.

What Dr. Stone has shown us is that, with very few exceptions—and he has defined those exceptions very clearly—anaerobic infection is cured by either appropriate operation or conversion of a wound to an open state, and that the use of possibly dangerous antibiotics allegedly aimed at anaerobes is not frequently necessary, and certainly not uniformly necessary.

DR. M. BERT MYERS (New Orleans, Louisiana): I rise to point out another fingerprint that bacteria have besides their odor.

(Slide) This is a pus-soaked bandage under normal light. The next slide is the same bandage under ultraviolet light, and the brilliant fluorescent pigment that you see there is one described by Dr. Polk and others which emanates from certain strains of pseudomonas bacteria.

(Slide) This shows another pus-soaked bandage under UV light in which a brilliant red fluorescent pigment was seen. On this we were unaware of the source until (slide) it was identified by Dr. Bornside as a *Bacteroides melaninogenicus*, one of the anaerobes which produces a fluorescent pigment both in vitro and in vivo.

We have seen this fluorescent bacterium in 27 cases now, either pus or, more commonly, in perineal gangrene; a very serious infection which is best treated by radical debridement, not antibiotics. We had around 80% mortality in this, until we began recognizing it early and doing radical debridement.

This is just a simple trick that enables you to suspect the bacteria very early and institute appropriate therapy.

DR. H. HARLAN STONE (Closing discussion): With regard to the duration of antibiotic therapy, five days was selected because most surgeons give antibiotics for a minimum of three and a maximum of seven days.

I appreciate Dr. Myers' comments regarding fluorescence of bacteria. We have been using the ultraviolet light to detect a lot of different things and, as he pointed out so nicely, it is quite helpful in identifying certain species of bacteria.

I did want to say one thing about Dr. Altemeier's cases. What he points out is so important. Intra-abdominal abscesses tend to localize in specific areas (in the pelvis, the gutters, or the subphrenic space). Communications between two or more of these may form a dumbbell or, as he has described, even a huge horseshoe. Independent drainage of each space is an absolute necessity.

Giant Horseshoe Intra-abdominal Abscess

W. A. ALTEMEIER, M.D., W. R. CULBERTSON, M.D., J. P. FIDLER, M.D.

A study of 12 patients with giant horseshoe abscess of the abdominal and pelvic cavities seen at the Surgical Services of the University of Cincinnati Medical Center has emphasized the complexity and bizarre nature of these lesions. These infections represented a huge abscess or series of communicating abscesses extending from one subphrenic space along the corresponding paracolic gutter into the pelvis, up and along the opposite paracolic space, and into the other subphrenic space. Since these lesions occurred infrequently, they were often not recognized until they had become far advanced and had produced profound effects on the patients. The diagnosis was difficult and obscured by various factors including the postoperative state after laparotomy for complex diseases or serious injuries of the biliary tract, the genitourinary tract, or the alimentary tract. An important etiologic component of the formation of these giant abscesses was the continuing escape and collection of large volumes of fluid resulting from lesions of the biliary tract, postoperative hemorrhage, or an unrecognized large perforated peptic ulcer. Nine patients were treated successfully and 3 died. The many diagnostic and therapeutic problems presented by the patients with this interesting and complex lesion have emphasized the importance of earlier and more accurate diagnosis, early and adequate surgical drainage, intelligently applied antibiotic therapy and appropriate supportive treatment. Failure to recognize and drain effectively each of the component sections of this lesion led to continuing sepsis with prolonged morbidity, progressive debility, and death.

GIANT horseshoe abscesses of the abdominal cavity present unusual, interesting, and life-threatening clinical syndrome with unusual problems in diagnosis and surgical management.

Horseshoe abscess is the descriptive term generally given to large abscesses which occupy a horseshoe shaped position in the lower abdominal and pelvic cavities.^{1,2} The conventional abscess of this type usually begins in the right lower quadrant and extends down into the pelvis, across the pelvic cavity and up into the left lower abdominal cavity. It has not been associated with

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acute perforated appendicitis, but has been noted to arise as the result of various other initiating diseases such as penetrating wounds of the abdomen, acute diverticulitis, tubo-ovarian abscess, and perforated peptic ulcer.¹

Unlike the usual horseshoe variety, the giant horseshoe abscess represents a huge abscess or series of communicating or loculated abscesses extending from one subphrenic space along the corresponding paracolic gutter, into the pelvis, also along the opposite paracolic space, and into the opposite subphrenic space (Figs. 1 and 2).

Since these lesions have occurred infrequently, they have often not been recognized by the surgeon until they have become far advanced and have produced profound effects on the patient. At best, the diagnosis has usually been difficult and obscured by various factors including the postoperative state after laparotomy or complicated diseases or extensive injuries of the alimentary or genitourinary tracts.

A study of 12 patients seen on the Surgical Services of the Cincinnati General Hospital and the University of Cincinnati Medical Center has been made in an effort to gain additional information which would be useful in the most effective diagnosis and surgical management of this interesting and complex lesion.

Clinical Materials and Methods of Study

During the 30-year period between 1944 and 1974, a total of 12 patients with a diagnosis of giant horseshoe abscess were seen at the Surgical Services of the Cincinnati General Hospital and the other hospitals of the University of Cincinnati Medical Center. Seven of these were male and 5 were female. The average age was 42.2 years, the youngest being 10 and the oldest 86 years (Table 1). Nine were Caucasian and 3 were Negro.

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1974, Boca Raton, Florida.

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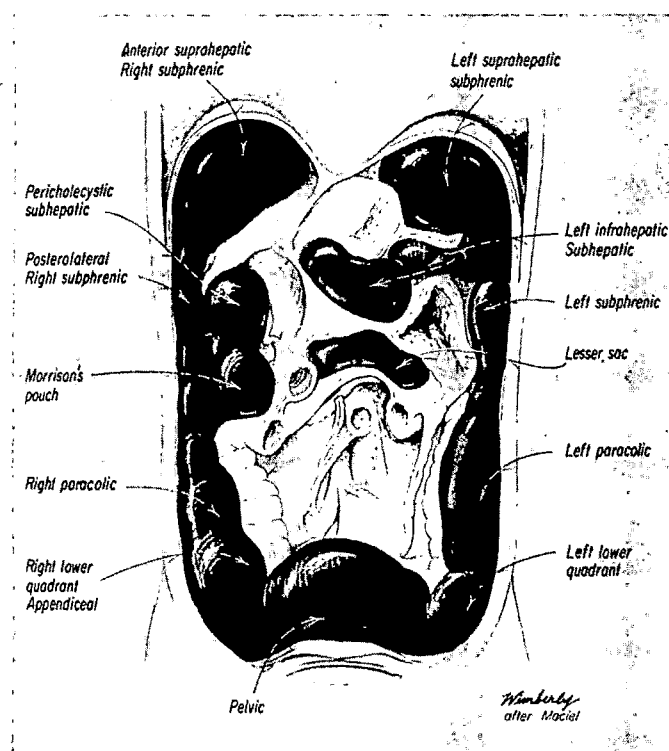


FIG. 1. Drawing showing the anterior view of the abdominal and pelvic cavity illustrating size, component parts, location, and extent of the giant horseshoe abscess.

Primary Sources. The primary source or initiating lesions of each of the abscesses are listed in Table 2. The most frequent source was the biliary tract, 5 of the 12 cases being of this type. In 3 of these patients the giant horseshoe abscess developed during a postoperative course following cholecystectomy (Fig. 3). Of the other two the source in one was a spontaneous perforation of acute cholecystitis and the other a rupture of the common bile duct secondary to fibrosarcoma.

The complexity of this giant horseshoe abscess arising post-cholecystectomy, and the problem associated with its diagnosis and surgical management are illustrated in the following case report.

TABLE 1. *Giant Horseshoe Abscess*

Case #	Age	Sex	Race
1	86	F	Negro
2	66	M	Caucasian
3	24	F	Caucasian
4	38	M	Negro
5	10	M	Negro
6	35	M	Caucasian
7	42	F	Caucasian
8	49	F	Caucasian
9	41	M	Caucasian
10	48	M	Caucasian
11	47	M	Caucasian
12	21	F	Caucasian

TABLE 2.

Primary Source or Initiating Lesion	Incidence	Living	Dead
1. Biliary Tract	5	4	1
A. Postoperative Cholecystectomy	3		
B. Perforation of Gallbladder or Common Duct	2		
2. Genital Tract	3	3	
A. Hysterectomy	2		
B. Adnexal Suppuration	1		
3. Colon	2		2
A. Gunshot Wound	1		
B. Carcinoma with Perforation	1		
4. Perforated Appendicitis	1	1	
5. Perforated Peptic Ulcer	1		1
	12	8	4

Case Report

R. C., a 35-year-old Caucasian man, had had a routine cholecystectomy without drainage and appendectomy performed in another city on 9/24/70. Two days postoperatively he developed a spiking fever to 102.6F. He then was started on Achromycin, 250 mg qid. A chest film on 9/30/70 revealed a density in the left lower lung interpreted as a pneumonia. On the sixth postoperative day drainage evidently developed spontaneously through his right subcostal incision. The drain-

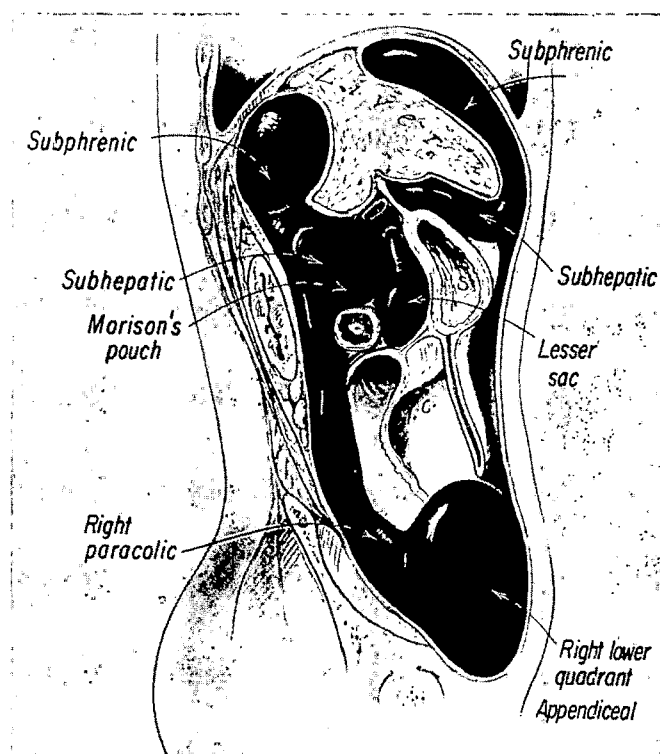


FIG. 2. Drawing showing the right sagittal view of abdominal and pelvic cavities and depicting the positions and variable depths of the same abscess as illustrated in Fig. 1.

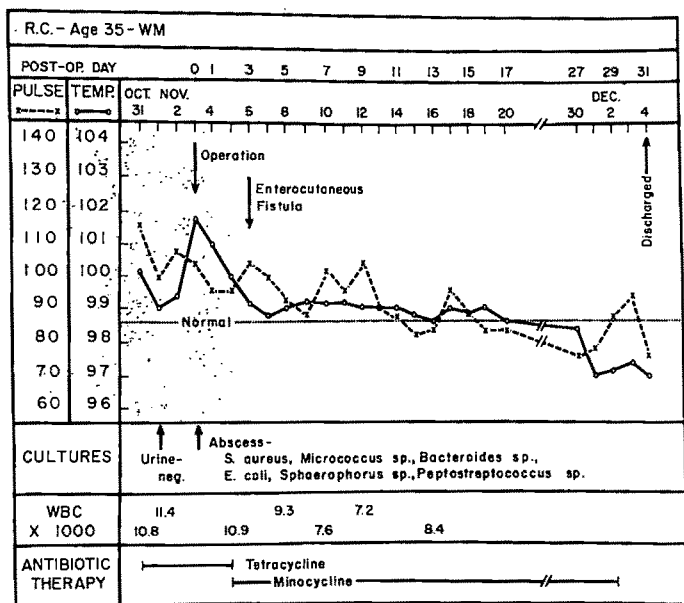


FIG. 3. Chart depicting the clinical nature, the treatment, and course of a 35-year-old man with a giant horseshoe abscess which occurred postoperatively after cholecystectomy without drainage.

age continued but gradually decreased over a period of approximately three weeks. He continued to be febrile, however, and on 9/30/70 the Achromycin was changed to Prostaphlin in dosages of 500 mg qid. This was discontinued on 10/7/70. X-ray continued to show evidence of pneumonia in the left lower base and air fluid levels were noted in the left upper abdominal quadrant. On 10/9/70 chloramphenicol in dosages of 500 mg qid was started. Chest fluoroscopy showed the left diaphragm to be elevated with limited excursion suggesting subphrenic infection. On 10/17/70 the patient was discharged to his home. He continued to be

febrile, however, and had hard bed-shaking chills on several occasions. He was readmitted to the hospital on 10/20/70 and a diagnosis of left subphrenic abscess made. This was drained and 600 cc of purulent material obtained. He was then started on Colymycin 150 mg bid intramuscularly. The patient continued to run a fever to 101F and Loridine was then started on 10/28/70 giving 1 gm bid along with Vibramycin 100 mg bid. Cultures of the abscess material revealed *E. coli* sensitive to chloramphenicol, Colymycin, and Kanamycin. Because of his continued febrile course, the patient was referred to the senior author of this report for further surgical management.

Physical examination revealed a well-developed, thin, Caucasian man who appeared to be chronically ill. His temperature, pulse, and respiration were 100F, 100, and 16. Blood pressure was 120/80.

There are decreased breath sounds at the left base with dullness to percussion. Breath sounds on the right were clear. Examination of the heart showed normal sinus rhythm without murmur. Abdominal examination showed moderate distension and evidence of a recent right subcostal incision, and a left upper quadrant draining incision. Bowel sounds were normal and no masses felt. There was tenderness in the right lower quadrant below the gallbladder incision.

On rectal examination a mass was palpable anteriorly being approximately 7 cm in diameter, slightly tender and compressible.

Laboratory Data. The admission CBC revealed Hgb. of 11.0 gm., Hct. of 33 vol.%, WBC of 10,300/cu. cm., and a differential which included 50% polys and 6 bands.

Chest x-ray revealed moderate collapse of the left lower lobe with elevation of the left diaphragm and minimal pleural fluid. Beneath the left diaphragm was a large air fluid area which was separate from the gastric air bubble. The splenic flexure of the colon was displaced inferiorly. The sigmoid was displaced out of the pelvis secondary to a central and right lateral large pelvic mass. There was a prominent extrinsic compression of this on the cecum.

Hospital Course. After preoperative evaluation a diagnosis of giant horseshoe abscess was made and the patient was prepared for operation. Large left subphrenic, left and right left quadrant and pelvic abscesses were evacuated with the release of a large amount of purulent material from these areas. The patient was placed on Minocycline on

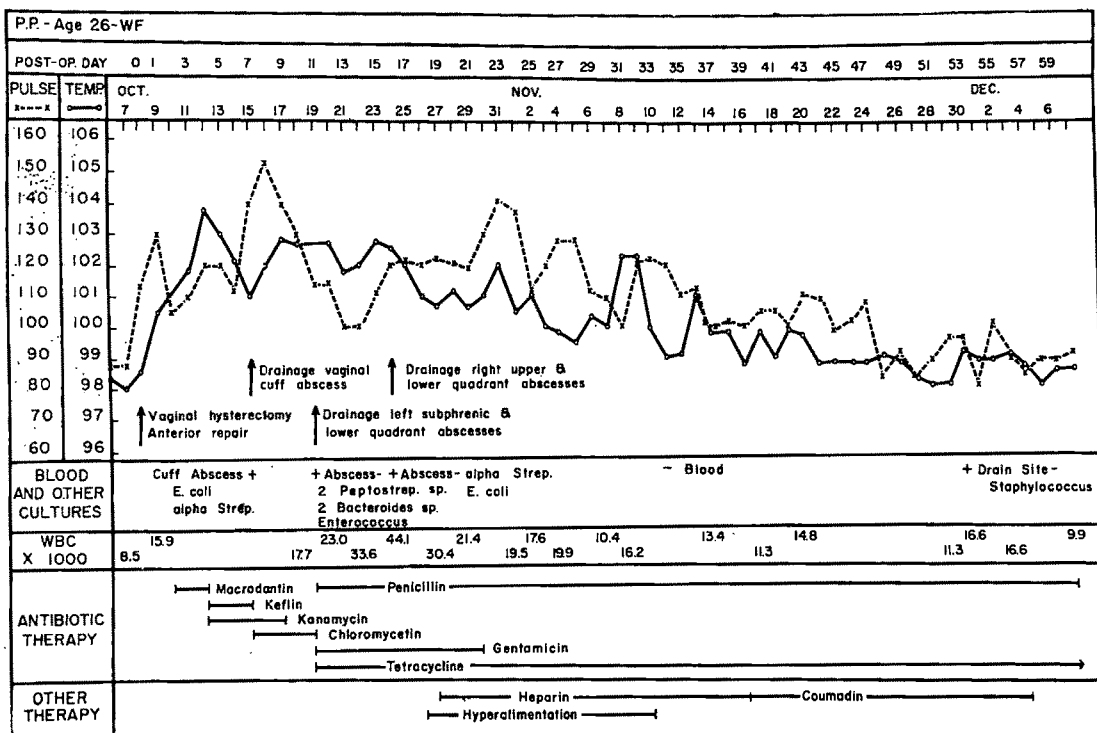


FIG. 4. Chart showing course of a 26-year-old woman who developed a giant horseshoe abscess in the postoperative period following vaginal hysterectomy complicated by serious abdominal hemorrhage.

TABLE 3. Length of Hospitalization and Incidence of Septicemia

Case #	Days in Hospital	Septicemia
1	17	E. coli
2	54	E. coli, Cl. perfringens
3	65	None
4	68	None
5	31	E. coli, Salmonella
6	34	None
7	56	None
8	58	Pseudomonas, Candida
9	36	None
10	10	E. coli, Bacteroides
11	61	E. coli
12	27	E. coli

11/5/70. The second postoperative day gas and stool were noted to be draining from the right lower quadrant stab wound and this was ascertained to be associated with an enterocutaneous fistula from the mid-portion of the small intestine.

During the remainder of his hospital course the patient's condition progressively improved with gradual decrease in the right lower quadrant drainage and healing of the enterocutaneous fistula (Fig. 3). Four weeks and 3 days postoperatively the patient was discharged and doing quite well and with his wound healing.

The next most frequent source was the female genital tract, with two of the abscesses occurring during the postoperative state for hysterectomy.

In one the operation was a vaginal hysterectomy which was complicated by postoperative hemorrhage, and in the other the hysterectomy was done intra-abdominally for uncontrolled postpartum hemorrhage (Fig. 4).

The following case report illustrates a case of giant horseshoe abscess arising from a pelvic source. It illustrates the problems it presented in diagnosis and management.

P.P., a gravida IV para IV 26-year-old Caucasian woman, was admitted on 10/6/71 to the Obstetric-Gynecology Service of the Cincinnati General Hospital for surgical sterilization. Physical examination was within normal limits except for first degree cystocele and uterine descensus. The uterus was anterior, soft, and of 6-8 weeks size of pregnancy. Preoperative laboratory results were normal including a

hematocrit of 41 vols.%. A vaginal hysterectomy and anterior repair were performed on 10/8/71. Twelve hours postoperatively a decreasing hourly output of urine, a pulse rate of 140 per minute, and vomiting were noted. A unit of blood was given when the hematocrit was found to be 31 vols.%. A second unit was given at 48 hours when the hematocrit was 28 vols.%. The patient's temperature rose to 103.8F and the white blood count to 16,000 by the fourth postoperative day. On the seventh postoperative day a large pelvic mass was drained of approximately 300 cc of thick pus through the vaginal cuff. The patient became increasingly toxic, however, and was thought to have a septic pulmonary embolization. Spiking fevers, tachycardia, a pericardial friction rub, and abdominal ileus became evident. Bilateral pulmonary infiltrate and pleural effusion were noted on chest films. Marked serum electrolyte disturbances were determined including a bilirubin of 3.1 mg.%, albumin of 2.2 mg.%, LDH of 260 mU/ml, calcium of 6.5 mg.%, sodium 124 mEq/L, potassium of 3.6 mEq/L, chloride of 87 mEq/L, BUN of 5 mg.%, and a prothrombin time of 30%. The white count had risen to 24,000 and on the eleventh postoperative day, surgical consultation was requested in regard to the possible need of vena caval ligation for the pulmonary infarct.

Examination of the patient then revealed exquisite tenderness over the 12th left rib and an adjacent mass to the left iliac crest. The patient was transferred to the Surgical Service and left subphrenic, left lower quadrant, and pelvic abscesses were drained on 10/19/71. The temperature elevations subsided for 36 hours when they again began to spike. Large right quadrant and right upper quadrant abscesses were then recognized and drained on 10/24/71 (Fig. 4).

The patient required no further operative intervention, but did require 15 days of intravenous hyperalimentation and 37 days of anticoagulation. She had received Keflin, Kanamycin, and chloramphenicol while on the Obstetric-Gynecology Service. On the Surgical Service and during the drainages of the components of her giant horseshoe abscess, she received 39 days of penicillin, 12 days of Gentamicin, and 57 days of tetracycline therapy. Bacteriologic report included *E. Coli*, alpha *Streptococcus*, *Enterococcus*, three species of *Bacteroides*, and two species of *Peptostreptococcus*. She was discharged on oral tetracycline therapy after a 65-day hospital course.

The giant horseshoe abscess was thought to have risen from a large pelvic and abdominal infected hematoma postvaginal hysterectomy. Her course was further complicated by multiple septic pulmonary emboli.

In the two abscesses developing from colon lesions, one was a gunshot wound of the abdomen with multiple perforations and the other a perforation of carcinoma of the transverse colon.

The remaining two cases followed episodes of acute perforated appendicitis and acute perforated peptic ulcer with delayed diagnosis and severe septicemia.

Clinical Picture. The clinical picture was that of a seriously ill patient with persistent spiking fever, rapid pulse, and general debility. Peaks of temperature were above 104F in 6 of the 12 patients, and the average high temperature was 103.3F.

Abdominal distention was noted in varying degrees in all patients, and was noted to be prominent in 7. Abdominal pain was present in only 8 or two-thirds of the cases, but tenderness to palpation was noted in the right upper quadrant, left upper quadrant in flank areas in 7 patients and right lower quadrant in 12, and the right lower quadrant in 6. A bulging mass on rectal or pelvic examination was found in nine. In general the pain and tenderness was

TABLE 4. Abscess Cultures

Microorganism	Incidence
E. coli	12
Bacteroides	10
Peptostreptococcus	9
Pseudomonas	4
Klebsiella	2
Enterococcus	2
Cl. perfringens	2
Candida	2
Proteus	1
Salmonella	1
Hemolytic Staph. aureus	1
Micrococcus	1
Average: 3.6 per Case	

TABLE 5. *Operative Data*

Case#	Size of Abscess (cc.)	Additional Operations
1	Not recorded	1
2	1,000	2
3	300 (+?)	3
4	3,000	2
5	1,450	2
6	650 (+?)	2
7	5,000	3
8	4,000	2
9	950	4
10	1,500	4
11	7,500	2
12	4,000	3

not commensurate with the size and extent of the abscess (Table 5).

Gastrointestinal Hemorrhage. Serious gastrointestinal hemorrhage was a complication in 3 of the patients, all of whom had an associated gram-negative septicemia.^{3,4} Two of these 3 patients died during the septic shock and gastrointestinal hemorrhage period.

Laboratory data showed marked leukocytosis with a definite shift to the left, the average WBC being 26,391 and the highest and lowest being 44,000 and 10,300 per cubic millimeter.

The bacterial findings showed positive cultures of the pus obtained at operation in all instances.^{5,6,7} Twelve different species were identified, the average number being 3.6. Both aerobes and anaerobes were found as listed in Table 4. At least one strain of *Bacteroides* was found in 10 of the 12 patients, and the *Peptostreptococcus* in 10. *E. coli* was recovered from all 12 cases. There were 7 cases of septicemia documented by positive blood cultures as shown in Table 3. The *E. coli* was the most

frequent etiologic agent being found in 6 instances. Others included *Bacteroides*, *C. perfringens*, *Salmonella* and *Candida*. Although a diagnosis of intra-abdominal abscess was made in all instances, the recognition of the giant horseshoe type was delayed in 9 of the 12 patients. This resulted in the need for 1 to 3 other operations for drainage of other component parts of these composite abscesses. A total of 30 operations of this type were required (Table 5). Delay in diagnosis was also partly reflected in the overall length of hospitalization. The average duration of hospitalization was 43 days with the longest being 68 days (Table 3).

Size of Abscess. The size of the abscess was determined in part by the volume of its content. The average amount removed at operation in 11 of the 12 cases was 2,723 cc, the largest volume being 7,500 cc. It was unknown and not recorded in 12 cases (Table 5).

Chemotherapy. The chief agents used in the management of these patients is shown in Table 6. All patients received chemotherapy and a total of 15 agents were used, penicillin, Chloromycetin, Keflin, and Gentamicin being the most frequent. An average of 3.4 agents were given per case and as many as 7 were used in a patient but never concurrently.

There are 4 deaths in this series. Two were the patients with malignant tumors, one with perforated carcinoma of the transverse colon and the other with perforation of the common bile duct caused by fibrosarcoma. The other two deaths included a patient with a gunshot wound of the abdomen with multiple perforations and hemorrhage, and a patient with perforated peptic ulcer and septicemia.

Discussion

The clinical and laboratory experiences from this group of 12 patients has emphasized the complex and bizarre nature of the syndrome of giant horseshoe abscess of the abdominal and pelvic cavities. It represents a huge abscess or a series of communicating abscesses extending from one sub-diaphragmatic space, along the right paracolic gutter, into the pelvis, up along the left paracolic gutter, and into the other sub-diaphragmatic space.

It is noteworthy that 9 of these lesions occurred post-operatively, 3 after cholecystectomy, 2 after hysterectomy, one in association with a tubo-ovarian abscess, and the remaining 3 as complications of acute perforated appendicitis, perforated peptic ulcer, and gunshot wounds of the abdomen.

Considered from another standpoint, 5 of the 12 cases occurred as complications of biliary tract lesions in which large quantities of bile escaped into the abdominal cavity, collected along the horseshoe tract, and became infected. In 3 other patients, extensive postoperative hemorrhage was present, two following vaginal and abdominal hysterectomy and one following a gunshot wound involving

TABLE 6. *Chemotherapy*

Agent	Usage Per Case
Penicillin	7
Chloromycetin	6
Keflin	5
Gentamicin	4
Erythromycin	3
Tetracycline	2
Kanamycin	2
Minocycline	2
Colymycin	2
Prostaphlin	2
Achromycin	1
Streptomycin	1
Vibramycin	1
Loridine	1
Sulfadiazine	2
Average Number Per Case:	3.4

the vena cava, another occurring during the course of a large perforated peptic ulcer which went unrecognized for more than 3 days with the consequent collection of a large amount of gastric contents into the abdominal and pelvic cavities. These observations indicated that an important component of the formation of a giant horseshoe abscess was the continuing escape and collection of a large volume of fluid along the flow tracts and lowest points of the abdominal and pelvic cavities.

Patients with this syndrome regularly presented special problems related to prolonged delay in diagnosis, difficulty in recognizing and localizing the various parts of the complex abscess, the necessity of surgical drainage of each of its component areas, the complex bacterial etiology, the appropriate antibiotic therapy, and adequate supportive treatment.

DISCUSSION

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): Dr. Altemeier's paper is, of course, a very clear one, and we have had experience with an inverted horseshoe abscess in recent months; in other words, one beginning in the lesser sac as a complication of pancreatic abscess, and dissecting down both paracolic gutters. I can confirm for you that those patients do as badly on our service, or more so, than has been described in his own setting.

I would share with you one thing that we have learned about intra-abdominal abscess that presents a greater problem on our service, whether it be small or large. (Slide) We have a terrible time making the early diagnosis of intra-abdominal abscess after major trauma and/or complicated operations, and the reasons are multiple. First of all, as shown in these patients, temperature and leukocytosis are not dramatic; the leukocyte function tests are not nearly so definitive as has been promised; x-ray studies are often not diagnostic; the gallium scans have not meant all that we thought they might. Inevitably this is grossly obscured by the administration of broad spectrum antibiotics for a long time.

(Slide) We are beginning to recognize as a new face of unappreciated intra-abdominal sepsis organ failure; a classic example is oliguric renal failure, which we initially thought was due to hypotension, transfusion, or nephrotoxic antibiotics. As a matter of fact, the most common cause of oliguric renal failure on surgical services today is unappreciated Gram-negative infection, usually intra-abdominal abscess. We must be alert to this new sign of unappreciated intra-abdominal abscess.

(Slide) As made so clear by Dr. Eiseman's earlier presentation, organ failure, whether it's respiratory or renal or hepatic, that's associated with infection *never* gets well with supportive care, such as dialysis or with respirator suspect the bacteria very early and institute appropriate therapy.

DR. WILLIAM A. ALTEMEIER (Closing discussion): Dr. Polk has pointed out various factors that help to make this lesion even more obscure, and we certainly agree with them. One of the principal ones is antibiotic therapy, which may make an obscure lesion much more obscure.

We recognize organ failure as another important factor in both gram-negative and gram-positive infections. We are investigating this in my laboratory, using both endotoxins and exotoxins injected intravenously in animals and measuring their pathophysiologic effects.

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We are also working to tag exotoxins and endotoxins with radioisotopes, and we hope to begin soon the injection of those toxins to see if we can identify the target organs or tissues of these toxins and correlate the pathophysiologic effects with these findings.

I'd like to say something about *Bacteroides* and the anaerobic *Streptococcus*, or, as it's now called, the *Peptostreptococcus*.

In 1928, when I began working in Dr. William Wherry's laboratory in bacteriology, I was introduced to the *Bacteroides melaninogenicum*. We call it "*B. melaninogenicus*" now, and the man who discovered it was Dr. William Wherry. Working with this organism, I found that it was almost always growing in symbiosis with an anaerobic *Streptococcus*, and that it was very difficult to separate them. If we did separate them, in those days, the anaerobic *Streptococcus* or the *B. melaninogenicum* both died. But if they were grown together, they grew quite well.

In 1938, I showed that the *Bacteroides melaninogenicum* had been misnamed, that this pigment was not melanin, but hematin; and that the organism had extracted the hemoglobin from the media to produce the brownish-black pigment. This phenomenon was noted also in tissues or grey discoloration of necrotic tissues. The combined growth of *melaninogenicum* and the anaerobic *Streptococcus* should be kept in mind.

The so-called "*B. coli* odor," we reported in 1942 in the *Annals of Surgery*, was caused not by *B. coli*, but by the anaerobes, principally the *Bacteroides* and the anaerobic *Streptococcus*. You will be interested to know that when I first submitted this paper to the *Annals of Surgery*, it was turned down as being an incorrect observation, since everybody knew that the odor was due to *B. coli*.

We resubmitted it to the same journal, however, with protestations, and I'm glad to say that it was then published.

Just one last comment about fluorescent microscopy of the *Bacteroides melaninogenicum* and other *Bacteroides*. Mr. Stouffer in my laboratory has been working for the past year and a half on a method of developing a differential diagnosis of the presence of *Bacteroides* in areas of infection by means of fluorescent microscopy. It is now possible to make a diagnosis of this type of infection within a matter of a few hours after the specimen has been taken. This will save days of indecision and confusion on the part of the clinician in knowing for sure whether *Bacteroides* are present. As you know, it usually takes three to five days to get a culture report back from the laboratory. In other words, this method promises to permit a more rapid and more definitive diagnosis and earlier and better selection of antibiotic agents for the treatment of these cases.

Subcutaneous Extraperitoneal Repair of Ventral Hernias:

A Biological Basis for Fascial Transplantation

ERLE E. PEACOCK, JR., M.D.

Two fundamental biological differences between normal fascia and scar tissue are rate of collagen turnover and physical weave of collagen subunits. Both factors account for unsatisfactory results following ventral hernia repair unless scar tissue is excised and normal fascia used. Removal of scar and identification of normal fascia often require extensive dissection, entrance into the peritoneal cavity, and sometimes requires lysis of intestinal adhesions with occasional injury to bowel. Simple imbrication of the hernia sac, as in treatment of a direct inguinal hernia, without extensive scar excision usually results in recurrence of the hernia because of remodeling and attenuation of scar tissue. A new procedure, based upon the technique of direct inguinal hernia repair without opening peritoneum, has been performed on 12 patients with large ventral hernias. The procedure, performed entirely in a subcutaneous plane, involves imbrication of scar, transfer of a massive fascial onlay graft, and use of an internal stent. Patients have been followed for one to 5 years; there have been no recurrences. Inductive influence of the fascial transplant has been measured in two patients; a tenfold increase in net collagen synthesis and deposition occurs for at least one year following transplantation of fascia to an imbricated scar recipient area.

FASCIAL GRAFTS have been used in a variety of ways to reconstruct the abdominal wall. McArthur, Gallie, and Le Mesurier pioneered the use of fascial strips as biological sutures.^{5,8} Kirschner introduced the use of sheets of fascia to increase breaking strength of the repaired abdominal wall; Wangenstein used the distal portion of the tensor fascia lata as a pedicle graft with intact proximal blood and nerve supply to reconstruct inguinal and inferior abdominal wall defects.^{6,18} Modern surgeons, however, with the exception of a few such as Ravitch, have seemed less interested in biological grafts and more intrigued with artificial substances such as Marlex, tantalum and nylon—presumably because of ease of pro-

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curement.^{7,10,15,16} There seems to have been little interest in developing the use of biological grafts during the past two decades. Because artificial substances become fragmented with time and occasionally have to be removed, fascial grafts should not be discarded entirely, particularly if indications for using fascial grafts can be expanded and repair of abdominal hernias made less difficult. Recent studies in transplantation and wound healing biology have suggested theoretical advantages and technical modifications for the use of fascial transplants based upon biophysical and biochemical differences between naturally woven dense connective tissue and scar.⁷ The rationale for such modifications follows.

One of the striking differences between dense connective tissue synthesized and remodeled during healing of a wound and dense connective tissue found naturally in fascia and tendon is reaction or response to physical stress. Although there are exceptions such as surface scars in the pectoral region or upper extremity of young people, scar tissue predictably responds to physical stress by becoming thin and elongated.¹ With the exception of frank keloid and hypertrophic scar which are rare in the abdomen and lower extremities, scar tissue in the lower half of the body becomes attenuated and thin with passage of time and application of stress. In contrast, naturally occurring dense connective tissue such as fascia and tendon resist physical stress and may even become hypertrophic rather than attenuated.^{2,11} The mechanism of attenuation of scar tissue is not understood completely but probably involves longitudinal slipping of subunits; attenuation also may be the result of less than optimum physical weave and biochemical cross-linking during secondary remodeling. Naturally occurring dense

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connective tissue, such as that found in fascia or tendon, seems ideally oriented and woven to resist longitudinal slipping of fibers and fibrils and may even be molecularly organized to insure maximum inter- and intramolecular cross linking.

Another factor worthy of consideration for the reconstructive surgeon may be the nearly tenfold acceleration of rate of net collagen synthesis and deposition measured in fascial grafts following autogenous as well as allogeneic transfer.⁹ In this respect, free fascial grafts may be even more biologically active in the induction of collagen synthesis and deposition than a pedicle flap which has not been completely severed from nerve and blood supply. Consideration of fascia lata as a membrane internally organized to resist physical stress and biologically active in the induction of collagen synthesis and deposition adds a new dimension to the use of fascial grafts during repair of ventral hernias. Specifically, if a fascial transplant provides early mechanical support and late biological inductive control of synthesis and secondary remodeling of connective tissue, the repair of a ventral hernia could be accomplished in a subcutaneous plane similar to repair of a large direct inguinal hernia without opening the peritoneum. Following this line of reasoning, fascial grafts could be used as biological inductors and temporary splints to make the repair of *all* abdominal hernias technically easier and recurrence less frequent rather than using the grafts almost entirely as a substitute for missing fascia in large defects, as previously recommended.

Most surgeons agree that the major technical difficulty in repairing a ventral hernia is accurate identification of normal tissue.¹⁴ The center of the defect usually is a combination of subcutaneous fat, attenuated scar tissue, and underlying peritoneum. Simple imbrication of scar tissue and peritoneum invariably results in recurrence of a hernia unless imbricating sutures are placed lateral to scar tissue in naturally woven normal fascia. Surgical dissection of the hernia and identification of normal tissue in the lateral margins are important steps, therefore, in successful repair of ventral hernias by conventional means. In most hernias, it is necessary to open the peritoneum and dissect the full thickness of the abdominal wall in a lateral direction until normal fascia is encountered. Failure to make an accurate distinction between lateral scar tissue and normal abdominal fascia often causes the surgeon to repair the defect with wound repair tissue and practically assures attenuation and recurrence. This often repeated principle of hernia repair is relatively easy to expound but technically may involve several hours of fairly hard work, particularly if intestinal adhesions are encountered.

An alternative to opening the peritoneum and searching for normal fascial margins is based upon exploitation of physical and biochemical properties of fascia lata

rather than abdominal wall surgery. Considered in this way, advantages of fascial grafts are equally applicable to small and large defects as the hernia is virtually ignored and the critical tissue junction is lateral to the defect between superficial normal fascia and graft rather than between two dissected surfaces of the abdominal wall. Practical advantages of overgrafting an imbricated hernia are that dissection is easy because it is limited to a subcutaneous plane lateral to scar tissue and intra-abdominal complications can be reduced or eliminated because the peritoneum is not opened. Obviously, such advantages will be appreciated more when repairing large defects than during repair of a small hernia. If recurrence is less or even no worse than following conventional methods of repair, disadvantages of using a fascial graft for all repairs should be limited to procurement of the graft. The theoretical and practical advantages and disadvantages of fascial grafts used following simple imbrication of a ventral hernia to provide temporary structural strength and long-term biological induction of collagen synthesis and deposition have been studied in 17 patients. Six of the patients had two or more recurrences following repair by a competent surgeon.

Technique

The operative procedure consists of opening the previous cutaneous scar and reflecting lateral skin flaps to expose the lateral abdominal wall. Cutaneous scar should be incised, not excised, unless the scar also is thin and attenuated. For a long period of time, biochemical and biophysical conditions measured within a cutaneous scar seem superior to normal skin, as far as subsequent or secondary healing is concerned. After the skin flaps have been reflected, subcutaneous dissection is performed to expose normal abdominal fascia several centimeters lateral to the hernia. A ring of normal fascia surrounding the abdominal defect should be exposed by this maneuver. Exposure of normal fascia should be so far lateral to the central defect that there is no question about being external to the zone of attenuated scar. The regular right angle weave of shiny white fiber bundles identifies normal fascia accurately. The hernia sac is then imbricated with large non-absorbable sutures to produce normal contour of the abdominal wall (Fig. 1). Sutures should be placed far enough lateral to imbricate the hernia sac neatly but not so far lateral that significant tension is produced when the sutures are tied. No attempt should be made to place the sutures in normal fascia if doing so produces tension. The purpose of the imbricating sutures is to reduce the hernia and restore normal contour to the abdominal wall; in small defects it may be possible to place imbricating sutures in normal fascia without producing significant tension. If the repair of large hernias is stopped after imbrication of the sac, recurrence will take only a few days or weeks as most of the sutures probably

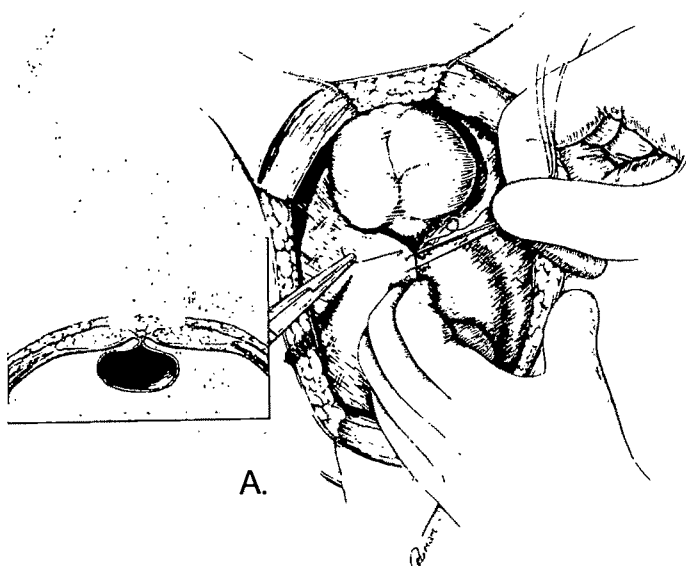


FIG. 1. Imbrication of central scar tissue to reduce peritoneal sac and restore normal contour of abdominal wall. In larger hernias, sutures will be in attenuated scar; in small hernias, sutures will be placed in normal fascia without producing significant tension.

will be in junctional scar tissue which will attenuate or tear when the stress of abdominal muscle contraction occurs.

After the abdominal wall has been contoured by imbricating sutures, an onlay fascia lata graft is applied for the reasons outlined above. The graft is removed from the thigh through either a curved longitudinal incision or two transverse incisions. The sheet of fascia is applied to the abdominal wall as an onlay skin graft would be sutured to a surface defect. (Fig. 2). Relatively large non-absorbable sutures, such as #2-0 silk, are used to attach

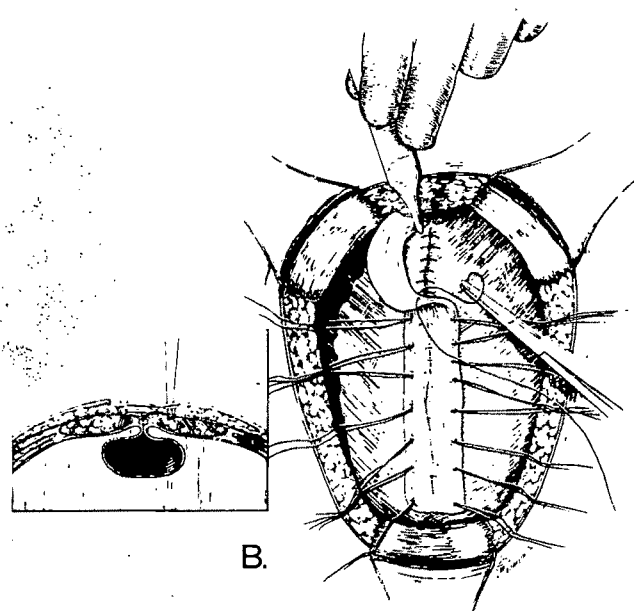


FIG. 2. Application of free fascia lata graft over imbricating sutures. The lateral sutures in graft must be placed in normal fascia.

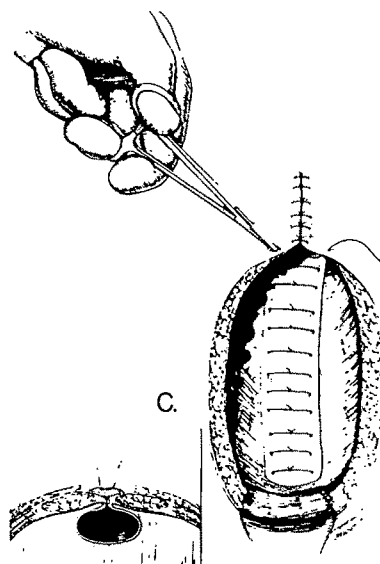


FIG. 3. Lateral sutures are tied across graft as in a stent fixation of a skin graft. Tying sutures across the graft helps obliterate dead space and provides mechanical support during healing.

the graft to the ring of exposed fascia surrounding the imbricated hernia sac. The ends of the sutures are retained to tie across the graft as in a stent fixation of a skin graft. Tying the sutures across the graft provides additional mechanical strength independent of the graft during the period of revascularization and early healing (Fig. 3). Finally, the skin flaps are reapproximated over the graft; hemovac suction has been used for 24 hours following repair of large hernias. A snug, but not constricting, abdominal binder has been used to obliterate space in the subcutaneous tissue following repair of small hernias or for a few days after removal of the hemovac tubes following repair of large hernias. The area of subcutaneous dissection is relatively large and collection of serum will occur if some measure is not taken to obliterate space and splint the skin flaps to the body wall during early healing.

The donor wound in the thigh is closed and a Penrose drain is inserted or a hemovac drain utilized to prevent accumulation of serum.

Results

The 17 patients in this series receiving onlay fascia lata grafts after imbrication of a ventral hernia sac have been followed between 2 and 5 years. There have been no recurrences in the area of the graft. One patient was found to have a small ventral hernia 12 months following repair with a fascial graft and was explored through the same incision. The graft could be clearly identified (Fig. 4); the hernia sac was 2 cm inferior to the margin of the graft. The conclusions were that the previous surgeon had misjudged the inferior extent of the defect at the time the graft was transplanted or that a progressive degeneration of the abdominal wall had occurred inferior to the grafted area. There was no indication that the graft had disintegrated.

FIG. 4. Fascial graft placed over imbricated suture line two years previously. Note that graft edge (at end of hemostat) can be easily identified. Sutures tied across graft are permanently enmeshed in scar and graft.



Two grafts have been exposed approximately one year following transplantation. One graft was in the patient described above with an inferior hernia; the other patient developed a renal tumor and was operated upon through a flank incision which was extended medially and superiorly to expose the graft. Both grafts were grossly discernible and did not appear to have changed in any significant manner. The stent fixation was firmly imbedded in new scar over the surface of the graft. The right angle weave of the original fiber bundles could be identified and did not appear to have been changed by transplantation. In one patient it was possible to compare total collagen and net rate of collagen synthesis and deposition in the graft before and after transplantation. Similar studies were performed in the other patient at the time of re-exploration; unfortunately, pretransplant studies were not performed in this patient and so comparison of the rate of synthesis before and after transplantation was not possible. In the patient in whom pretransplant data were available, net collagen synthesis and deposition was measured by the Peterkofsky-Diegelman method and reported as specific activity in disintegrations per minute per microgram of hydroxyproline.¹³ Pretransplant studies of the fascia lata showed 11.0 disintegrations per minute; one year later the graft showed 91.0 disintegrations per minute or a ninefold increase in rate of collagen synthesis and deposition. Total collagen in the specimens was measured by the Woessner technique.²⁰ The graft showed 12.258 micrograms of hydroxyproline per milligram dry weight of tissue before transplantation; one year later the graft had 8.426 micrograms of hydroxyproline per milli-

gram of dry weight of tissue. This finding strongly suggests that collagenolytic enzyme activity kinetics also were accelerated and that turnover of collagen in the fascia was increased following transplantation. The graft from the other patient showed 90.0 disintegrations per minute when analyzed for net collagen synthesis and deposition. Because pretransplant values for normal fascia on all specimens averaged approximately 10 disintegrations per minute, it seems likely that a significant increase in net collagen synthesis and deposition occurred in the second patient as well. Total collagen in this patient was 7.432 micrograms of hydroxyproline per milligram dry weight of tissue; the average total hydroxyproline value in pretransplant fascia is 8.426 micrograms of hydroxyproline per milligram of tissue. Thus a small reduction in total collagen appears to have occurred in this patient also. These measurements in patients reveal almost exactly the same findings as previously reported in fascial transplants under similar conditions in animals.⁹ Pre- and post-transplant electron micrographs of one fascial graft revealed preservation of the original parallel orientation of fibrils. Coarse fiber bundles also appeared by gross observation to have retained their original right angle weave.

None of the patients developed significant or prolonged donor site problems; the first 5 patients developed transient collections of serum which required drainage during the early postoperative period. Subsequent use of hemovac drains or penrose drains has seemed to eliminate this complication. There were no late sequelae in the donor site and none of the patients reported any disability

following removal of their tensor fascia lata. The two most serious postoperative complications were respiratory in one patient who had the lower chest immobilized by a constrictive dressing applied too high on the thorax, and drainage of the abdominal wound for several months requiring removal of an infected suture in another. In the patient with the infected suture, the graft was not affected and the hernia repair remained intact.

Operating time averaged one and a half hours with a minimum of 45 minutes and a maximum of two and a half hours. Abdominal distension, ileus, or other gastrointestinal complications were not observed in any of the patients.

Discussion

Two obvious objections to the use of a large fascial onlay graft and stent fixation to bolster an inadequate ventral hernia repair consisting only of imbrication of the peritoneal sac and scar are 1) production of a donor site wound in the thigh and 2) insertion of a relatively large amount of non-absorbable suture material. Other than a few minutes of extra operating time required to take the graft, the donor site complications can be dismissed. In a superb study of 57 patients followed from one to three and a half years after removal of large sheets of fascia lata, Dubiel and Wigren searched for disability which could be measured in the donor extremity.⁴ There simply was no disability in their patients and there was no disability in the patients reported in this paper. Moreover, recent studies comparing certain biochemical and biophysical effects of transplanting autogenous and allogeneic grafts reveal that, under the conditions of the experiments, there was no significant differences between allografts and autografts.⁹ If a reason exists, therefore, not to take an autograft, it seems likely from these studies that an allograft would perform equally well.

Because many ventral hernias are the result of abdominal wall infection, the objection to the use of stent fixation of the graft because of the relatively large amount of non-absorbable sutures required is more than theoretical.³ One of the patients in this series required removal of an infected suture. Because the graft apparently was not affected, however, it does not seem now that this complication is a serious deterrent to the use of an onlay fascial graft with stent fixation. Because a new fascia lata transplant does not have great tensile strength in all dimensions, and because preliminary imbrication is almost worthless from the standpoint of resistance to physical stress, a strong non-absorbable suture technique was thought to be worthwhile in providing physical strength during the first 3 to 4 weeks while the graft is becoming a part of the anterior abdominal wall. In some respects, the stent fixation acts as an ethylon mesh repair while the graft becomes attached to the abdominal wall and underlying central scar tissue. Since developing this technique,

the author has learned that Ravitch has recommended using fascial onlay grafts over peritoneal imbrications without stent fixation.¹⁵ Perhaps the stent fixation is unnecessary.

Practically every conceivable material has been used successfully and unsuccessfully to replace missing abdominal wall or bolster a repair consisting of direct approximation of the edges of a fascial defect. There has been recurrence following all types of repairs—a finding which supports experimental work and observations in human patients suggesting that a major connective tissue abnormality is present in some, if not all, recurrent abdominal and inguinal hernias previously repaired by competent surgeons.^{12,17,19} In patients where this is true, and it should be considered in all patients where recurrence follows repair by an adequate surgeon, a biologically active substance may offer advantages over artificial or inert materials. That fascia is such a biologically active membrane and that activity in the transplant is increased significantly by autogenous and allogeneic transplantation suggest theoretical advantages to the use of fascia over non-biological substances. Application of the graft through a subcutaneous plane without opening the peritoneum is attractive from the standpoint of reducing operative time and postoperative gastrointestinal complications. The results in the patients reported in this paper indicate that theoretical advantages pertaining to the inductive power of transplanted fascia are accompanied by practical advantages measured in terms of persistence of the repair, reduction of complications, and elimination of some technical difficulties. The procedure is recommended, therefore, on the basis of practical as well as theoretical advantages in the repair of ventral hernias of any size. Primary repair of a small hernia may be an exception but recurrent hernias of any size following repair by a competent surgeon probably represent some sort of local or general connective tissue abnormality and should, therefore, be considered for repair using biological as well as mechanical adjuvants.

Conclusion

Autogenous grafts of large sheets of fascia lata applied by a stent technique over imbricated scar and peritoneum offer theoretical biological and practical technical advantages when compared with non-biological substitutes.

Seventeen patients operated upon by the onlay-imbrication technique have not developed recurrences over a 2 to 5 year observation period and did not develop any significant postoperative gastrointestinal complications.

The use of relatively large amounts of non-absorbable suture material in a wound which has a high incidence of retained organisms appears at this time to be the major theoretical hazard of the procedure. In one patient in this

series, removal of an infected suture did not result in loss of the graft or recurrence of the hernia.

Acknowledgment

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DISCUSSION

DR. ASHBEL C. WILLIAMS (Jacksonville, Florida): I gave a paper many years ago before this organization at the time I was taken in. The subject was fascial transplants after the method of Dr. Edward Gallie. This was the last paper on the last day of the meeting. As I recall, Dr. Amos Koontz, Joe Hamilton and Calvin Klopp were the only ones considerate enough and loyal enough to stay and listen to it.

At that time I reported 54 inguinal hernias repaired with living fascia after the method of Dr. Gallie. I had talked with Dr. Gallie over the phone and had several letters from him prior to that time and ascertained that he still was completely sold on the method as he had originally presented it. This, I think, was in 1955.

Since that time I have had approximately 50 additional Gallie operations and to my knowledge there have been only three recurrences.

This operation has been done only on patients who had had hernia repairs previously or who had had huge hernias and were in very demanding physical lines of work where they were subjected to all types of stresses and strains.

At the time of the original paper I had followed some patients as long as 12 years postoperatively and quite a few of the original group have departed this earth because of age or other diseases, but only three, that I know of, have had recurrences of their hernia.

I have not been aware of all the erudite things that Erle Peacock has told us about what happens in the cellular compartments, etc., but I feel strongly that this fascial repair is the Cadillac of all hernia repairs.

After a brief experience with tantalum mesh in inguinal hernias, I gave this method up because the repairs were painful and if there was a recurrence the difficulty of correcting it was formidable.

On incisional abdominal hernias I use stainless steel or tantalum mesh and have been very impressed with the effectiveness and durability. I am sure, however, that fascia would do very well in these abdominal hernias, as it does in the groin. But the comfort in the groin of the fascia repair is not comparable with anything that I was able to accomplish with mesh. Some of the repairs encompass such a large area that I feel here that mesh would probably be preferable.

DR. ROBERT ZEPPA (Miami, Florida): When Dr. Peacock speaks, I

always learn something; but I remember calling him about a year ago about a problem with recurrent inguinal hernia. I had first occasion to see this gentleman for his third or fourth hernia repair and discovered that the first three had not been done to Cooper's ligament. So we did a Cooper's ligament repair, and six months later it was back.

That exhausted my therapeutic efficacy, so I called Erle, and he suggested putting in a large fascial autograft through the Cheatle Henry approach, which we did, which lasted six or eight months. On return to this inguinal area, no fascialata could be found, back to the peritoneum.

My question is this: Are there patients who have collagenolytic activity such that the application of fascialata, or other fascias, would be precluded because of their capability of dissolution, rather than the excitation of normal human collagen induced by such a graft? Thank you.

DR. ERLE E. PEACOCK, JR. (Closing discussion): Bob, you always get right to the point. That's one of the things we're studying: Can the graft get the disease, just like a transplanted kidney? Can it get glomerulonephritis and ruin the whole technical procedure?

This is premature for me to answer, though I promise you, within the next few years, enough data, I think, to help answer it. But I will say this now. We have two such patients such as yours. I think the groin situation is an entirely different matter, and collagenolytic activity in the groin is fierce. We have measured it, and it's fierce.

In the two patients in which we got recurrence from a massive graft, we were able to find that graft mechanically dislodged, rolled up, and it was due to the graft moving out of place. I couldn't find any evidence that the graft had actually gotten the disease, like the transversalis fascia did; and that's when we started to put it in like an airplane wing, from one lateral pelvic wall to the tip of the sacrum, to the symphysis pubis, across to the other wall, in a preperitoneal approach. But that's another subject.

With your permission, I'd just like to say that you asked just the question, and I promise that we will have some data that will satisfy you, both biochemically and mechanically; but now to say that I just really can't identify a patient who destroys a fascial graft that fast, and yours may be one that I wish was in my series, but we're bound to find one sooner or later like that if we keep looking and studying.

The Use of Mersilene® Mesh in Repair of Abdominal Wall Hernias:

A Clinical and Experimental Study

ELMO J. CERISE, M.D., RONALD W. BUSUTTIL, M.D.,
CLAUDE C. CRAIGHEAD, M.D., WILLIAM W. OGDEN II, M.D.

Use of synthetic materials in hernioplasty has been a controversial issue. In order to determine the influence of Mersilene® mesh on the strength of healing abdominal wounds and its effectiveness in repair of hernia, experimental and clinical studies were undertaken. Experimental study included 175 male rats divided into three groups subjected to either: 1) an incision made only through the skin and closed with 3-0 silk sutures; 2) a 2.5 cm midline incision through the musculature and peritoneum closed with 2-0 Mersilene® suture; or 3) the same procedure as group 2 with the addition of a Mersilene® mesh onlay graft. Bursting strength of abdominal wounds was determined in all groups at intervals. Wounds of the group treated with the mesh exhibited significantly greater ($P < 0.01$) bursting strengths. Clinical trial consisted of 100 consecutive adult patients in which an onlay graft of Mersilene® mesh was used in the hernioplasty. Mesh was used as an adjunct in patients with: 1) large ventral hernias; 2) direct hernias resulting from severely attenuated transversalis fascia; 3) indirect hernias associated with a large internal ring and a weak posterior inguinal wall; or 4) combined direct and indirect hernias. All were followed for a minimum of one year to determine incidence of complication and rate of recurrence. This study suggests that: 1) Mersilene® mesh increases the strength of healing abdominal wounds in rats; and 2) repair of large hernias with Mersilene® mesh results in an acceptable morbidity and a lowered rate of recurrence.

THE CONTROVERSY regarding the best method for repair of hernia is probably as old as the malady itself,²⁰ undoubtedly because the problem of herniation seems to be a simple mechanical one for which there should be a sure method of repair. Theoretic simplicity of a problem does not always result in a perfect solution. Thus, despite surgical advances, the foolproof herniorrhaphy still eludes us. Consequently, there has arisen a legion of suggestions to improve upon the repair of hernia. These

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proposals have suggested variations in the anatomic arrangement of the repair,¹¹ use of autogenous or homologous fascial tissue,⁶ or placement of prosthetic materials to bolster the herniorrhaphy when the patient's own tissues seem to be inadequate.^{3,17}

Use of prosthetic materials in repair of hernia has been accepted with variable enthusiasm throughout the years. Reports evaluating the use of such materials primarily concern the rate of infection and the host's tolerance after placement of synthetic materials. Some^{8,16} have directed attention to recurrence of hernia following the use of prosthetic materials. As emphasized by Zimmerman,¹⁹ in most instances of inguinal hernia, the actual rate of recurrence is far greater than that reported. Some factors which make it difficult to obtain accurate statistics are: 1) inadequate postoperative evaluation; 2) evaluation based on a questionnaire or another physician's examination; 3) variable criteria for recurrence; or 4) death of the patient. In our search of the literature, we found few reports^{10,14,15} in which rate of recurrence was determined in every instance of examination by the operating surgeon. These data are summarized in Table 1. Also, there has been little documentation that prosthetic materials do indeed enhance wound strength.^{2,4} The present experimental study and clinical trial was undertaken to determine if the use of mesh would: 1) contribute to the strength of healing of a wound; and 2) decrease the rate of recurrence in difficult hernias without increasing the incidence of complications.

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TABLE I.

	Shuttleworth ¹⁵ & Davies	Marsden ¹⁰	Nielsen ¹⁴ et al.
Year	1960	1962	1972
Cases	335	1602	343
Followup	4-12 yrs.	3 yrs.	2-12 yrs.
Total recurrences	14.3%	6.8%	14.5%
Indirect	14.2%	5.2%	
Direct	18.3%	7.4%	14.5%
Recurrent		19.0%	

Experimental Study

Methods. Male Sprague-Dawley rats were used. These animals weighed 150 to 200 grams at the beginning of the study. The animals were housed in an air-conditioned room maintained at a uniform temperature of 75F, and were fed a standard pellet diet with water *ad lib*. After the introduction of anesthesia with sodium pentobarbital, the rat's abdomen was clipped of hair and painted with iodine. Animals were then assigned to three groups.

Group 1 comprised 35 rats which were subjected to a sham operation in which only an incision in the skin was made and then closed with 3-0 silk.

Group 2 consisted of 70 animals in which a 2.5 cm midline abdominal incision was made through the musculature and peritoneum. This incision was then closed with 2-0 Mersilene® interrupted sutures placed exactly 5 mm apart and 5 mm from the edge of the wound. The skin was closed with a continuous suture of 3-0 silk.

Group 3 consisted of 70 animals which were treated as group 2. In addition, prior to closing the skin, a 2.0 cm x 3.5 cm rectangle of Mersilene® mesh was applied as an onlay graft over the abdominal incision. This graft was secured with a continuous suture of 2-0 Mersilene® (Fig. 1). All animals were returned to their cages to recover.

Bursting strengths of the intact abdominal walls of group one and of the abdominal wounds of groups 2 and 3 were then determined 3 and 5 days, and 1, 2, 4, 8 and 16 weeks postoperatively. The procedure used for determining bursting strength was a modification of that described by Myers¹² in which the abdominal wall is placed in a pneumatic tensiometer. The wound is then exposed to a steadily increasing amount of air pressure until dehiscence occurs. When disruption of the wound occurs, an immediate drop in pressure is recorded on a Sanborn pressure recorder, Model 127. Bursting pressure of the wound was the maximum pressure in pounds per square inch (PSI) needed to disrupt the wound or normal abdominal wall. This method for testing wound strength was selected because exposure of the wounds to an increasing internal pressure is a fairly close approximation to the elevations of intra-abdominal pressure which weaken re-

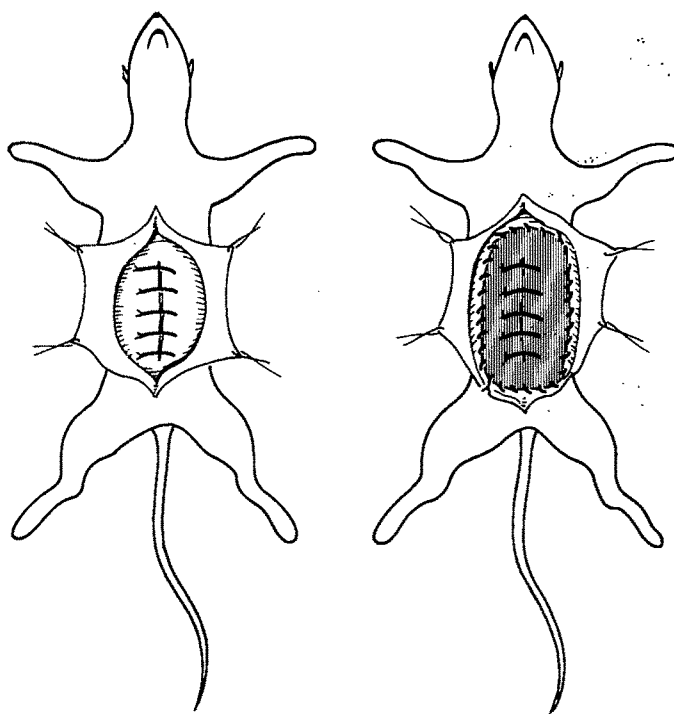


FIG. 1. Technique used to close the musculo-peritoneal defects in two groups of experimental animals. On the left the defect is closed without a graft; on the right, an onlay graft of Mersilene® mesh is added.

pair of a hernia. Furthermore, since this study was an attempt to simulate the conditions under which a herniorrhaphy might break down, all sutures except those in the skin were left in place when the bursting strength was determined. Animals which showed evidence of infection were discarded. The mean of the bursting pressures at each test period was calculated and the significance of difference between groups was determined by the Student *t* test.

Results

The results of studies in which the bursting strengths of wounds in the abdominal wall of rats were determined are summarized in Fig. 2. In sham-operated animals bursting strength of unwounded abdominal walls increased steadily throughout the time periods studied. During the 16 weeks of testing time, the rats in our study doubled in weight. This increase in weight paralleled the increase in bursting strength. By the end of the testing period, the bursting strength of the abdominal wall of sham-operated animals was twice that seen at the third postoperative day: 32.4 PSI vs. 16.4 PSI, respectively. These findings are consistent with the results of Levenson and co-workers⁹ who reported that the breaking strength of unwounded skin of animals of different ages is directly related to the weight of the animals.

Until the seventh postoperative day, abdominal wounds which were closed with Mersilene® sutures alone

*Ethicon, Inc., Somerville, New Jersey.

**Polyester fiber mesh, Ethicon, Inc., Somerville, New Jersey.

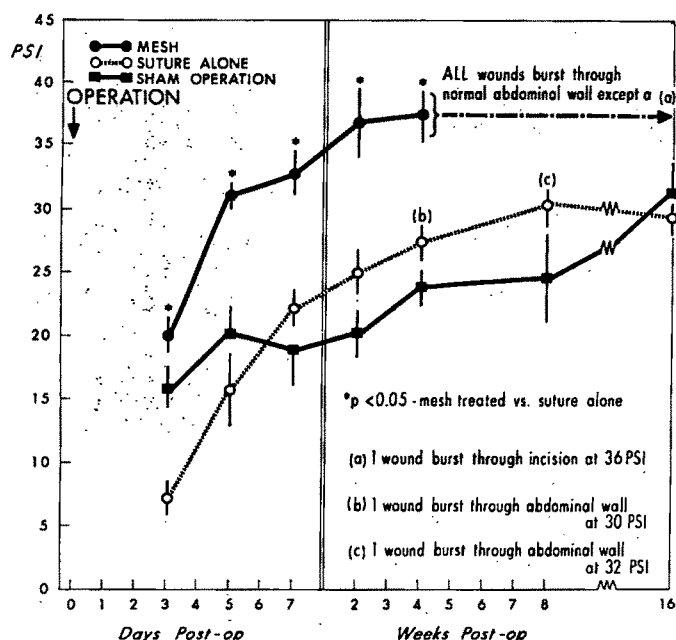


FIG. 2. Bursting strengths of rat abdominal walls in experimental animals.

(group two) exhibited significantly lower ($P < 0.01$) bursting pressures than did unwounded abdominal walls of sham-operated animals. However, from 7 days to 8 weeks postoperatively, wounds of Group 2 animals appeared stronger than did the normal abdominal wall of Group 1 animals.

Wounds which were repaired with the addition of an onlay graft of Mersilene® mesh (Group 3) exhibited significantly greater ($P < 0.01$) bursting pressures at all time periods tested than did the wounds of animals repaired with Mersilene® suture alone. The superiority of the

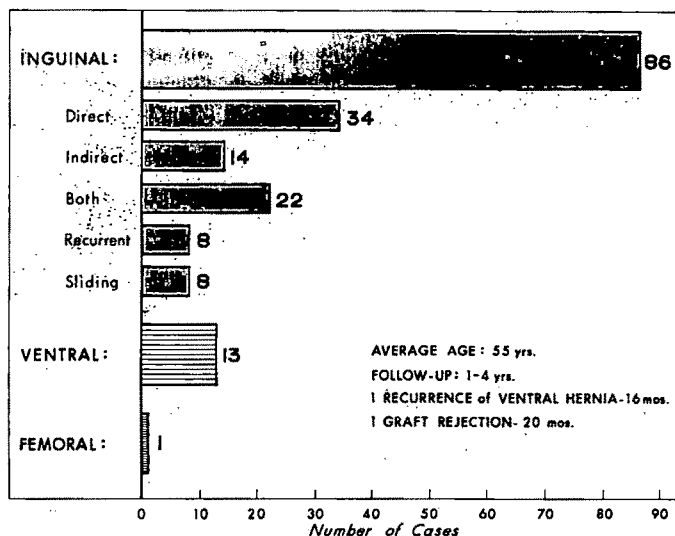


FIG. 3. Graph showing distribution of patients in which Mersilene® mesh was employed in repair of hernia.

GROIN HERNIA REPAIR

(INDIRECT HERNIA WITH LARGE INTERNAL RING)

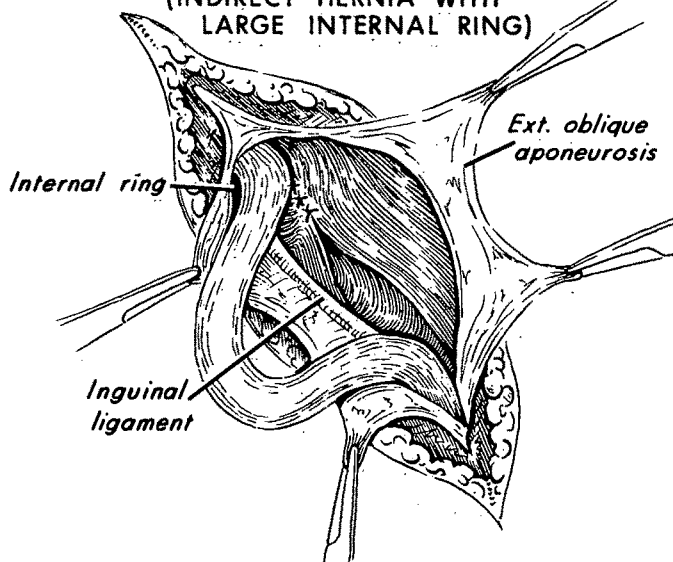


FIG. 4. Initial step in repair of indirect hernia followed by procedure illustrated in Fig. 6.

mesh (Group 3) compared to the suture alone (Group 2) appeared most apparent in the first postoperative week, when the former group was approximately two to three times stronger than the latter group. After postoperative day 7 and throughout the remainder of the test period, wounds of the animals in Group 3 were 50 to 60 per cent stronger than wounds of the animals in Group 2. After the eighth postoperative week, the majority (23 of 30) of abdominal wound disruptions in animals in Group 3 occurred through adjacent normal abdominal wall instead of through the wound. Only two out of 30 animals in Group 2 exhibited preferential disruption of the unwounded portion of the abdominal wall at these same time periods.

Clinical Trial

For a 3½-year period ending in December 1973, Mersilene® mesh was used as an onlay graft in the repair of 100 hernias in adults. The average age of these patients was 55 years. Mersilene® mesh was selected because we considered it to have many favorable properties—it is readily available, inexpensive, soft, pliable, relatively inert, well tolerated by tissues, maintains good tensile strength, and does not unravel at the cut edges. This mesh was used as an adjunct to the hernioplasty in patients with: 1) large ventral hernias; 2) direct hernias resulting from severely attenuated transversalis fascia; 3) indirect hernias associated with a large internal ring and a weak posterior inguinal wall; or 4) combined direct and indirect hernias. Fig. 3 depicts the distribution of patients in which Mersilene® mesh was employed in the repair of

GROIN HERNIA REPAIR (DIRECT HERNIA)

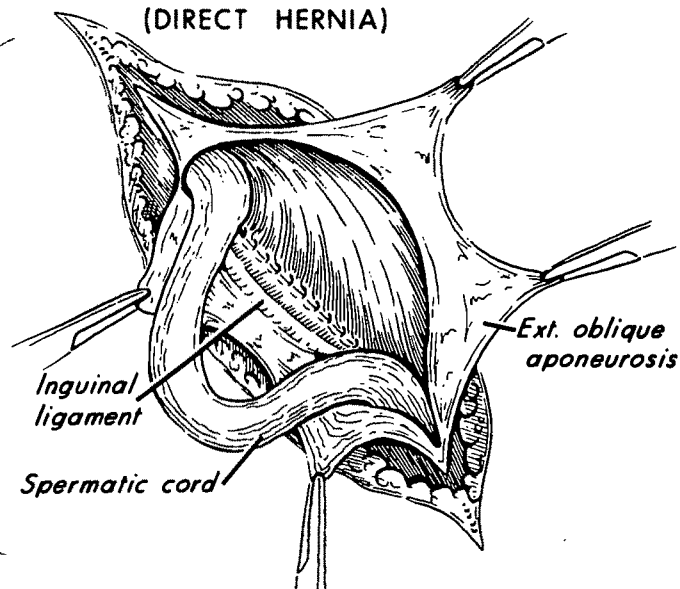


FIG. 5. Initial step in repair of direct hernia followed by procedure illustrated in Fig. 6.

hernia. It also shows the relative frequency of its proportionate use in each type of hernia.

Technique of repair varied slightly depending on the anatomic defect and the choice of the surgeon. As a first step in repair of indirect hernia, the sac was ligated high, and the internal ring closed partially (Fig. 4). In repair of direct hernias, the sac was inverted and the transversalis fascia sutured over it (Fig. 5). In both types of groin hernia, the floor of the inguinal canal was then covered by an onlay graft of Mersilene® mesh sutured circumferentially in the following manner (Fig. 6): beginning at the

GROIN HERNIA REPAIR

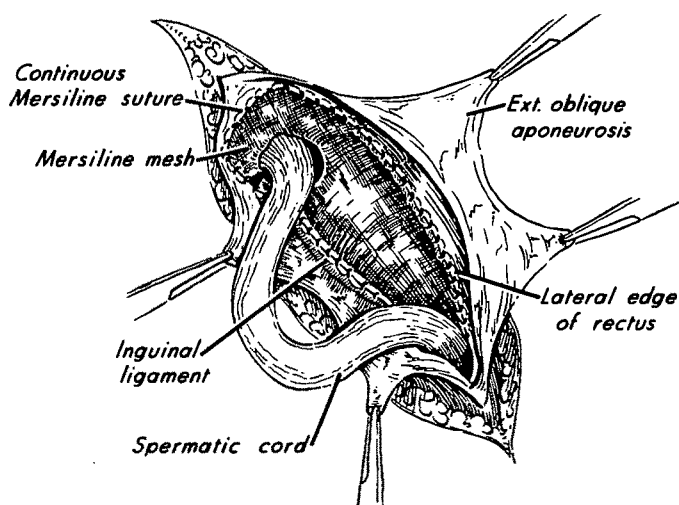


FIG. 6. Final steps in repair of groin hernia.

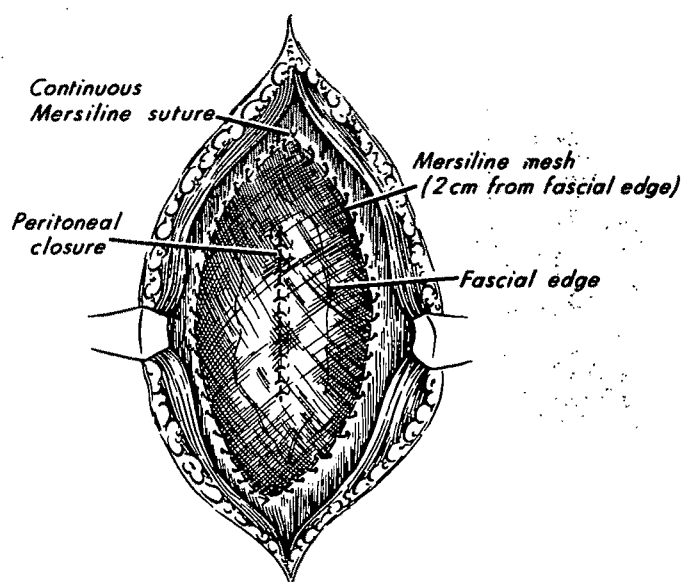


FIG. 7. Method used for repair of ventral hernia.

pubic tubercle, the mesh was sutured sequentially to the conjoint tendon, lateral edge of the rectus sheath, internal oblique muscle, inguinal ligament circumscribing the internal ring, and finally to the pubic tubercle. Mersilene® or Prolene® suture material was used throughout the procedures.

In the repair of ventral hernias (Fig. 7), the fascia was approximated, if possible, without undue tension. Otherwise, only the peritoneum or edges of the sac were closed, and the mesh was sutured in an onlay fashion over the defect. The mesh was cut so that it extended 2 cm beyond the fascial edge. Again only Mersilene® or Prolene® sutures were used. Suction with sump drains was used postoperatively in almost all cases of ventral hernia. Prophylactic antibiotics were not used unless a large amount of drainage was expected.

All patients were followed for a minimum of 1 year and a maximum of 4½ years. During this period there was one recurrence of a ventral hernia 16 months following repair. Only one serious complication consisting of recurrent abscesses and sinus formation occurred 20 months after operation. This patient had repair of a large sliding hernia of the groin which healed uneventfully and showed no evidence of infection for more than 1½ years. In this instance there was a past history of furuncles in the pubic area, and possibly the Mersilene® graft should not have been used.

Discussion

Our experimental and clinical investigations provide evidence that Mersilene® mesh can be used effectively in the treatment of difficult hernias with an acceptable rate

*Ethicon, Inc., Somerville, New Jersey.

of complication. Our results of bursting strength in abdominal wounds of rats support the hypothesis that mesh adds to the strength of a healing wound. The added strength which the mesh provides would appear particularly important in the first 7 to 10 postoperative days when the most important factor contributing to strength of the wound is the suture material.¹ As shown in our study, the strength imparted by sutures alone in the early postoperative period is quite low and disruption of the wound in experimental animals occurred quite readily. After 10 to 12 days, the presence of sutures contributes little to the strength of the wound; the primary determinant of tensile strength is collagen deposition.¹³ However, when local tissues are inadequate for repair of the wound, good fibroblastic proliferation is retarded and strength of the wound will continue to be low. Our data indicate that strength of the wound is markedly enhanced in these late periods by the addition of Mersilene® mesh. The reasons for this are twofold: 1) the mesh itself has good tensile strength and provides added support to a weak scar, and 2) the mesh initiates a tissue response with subsequent ingrowth of a dense infiltrate of fibrous tissue which contributes to strength of the wound.^{16,18}

Our finding that a healing wound bursts at a higher pressure than unwounded abdominal wall is not a new observation. Several investigators have reported this result while testing the bursting strength of the abdominal wall of dogs⁷ and guinea pigs.¹ Although we did not measure collagen content of the wounds, an explanation for the higher bursting pressure of wounded abdominal wall is that a healing wound has larger amounts of collagen by 14 days post wounding than does the uninjured tissue of the same type.

Despite the enhanced wound strength which was observed in the Mersilene®-mesh-treated group of our experimental model, it is difficult to extrapolate with any certainty the relationship between increased strength of the abdominal wall of the rat and prevention of recurrence of hernia in man. Furthermore, the true incidence of infection, erosion into adjacent tissue, or host rejection is difficult to evaluate in the rat model. However, it should be noted that throughout our experimental period, the group treated with mesh did not show an increase in these adverse reactions. Moreover, there are a group of rats which have had Mersilene® onlay grafts for over 11 months without untoward effects.

Although our clinical experience with the use of Mersilene® mesh as an onlay graft is admittedly small, the results to date have been gratifying. The rate of complication (1%) with the use of mesh has been quite acceptable and in accord with the rate of complication following routine herniorrhaphy which has been reported.⁵ Moreover, the one infection which occurred in the present series was probably a result of an error in judgment since mesh was used in a patient with recurrent furun-

culosis of the groin. Using the technique described, the rate of recurrence has been 1 per cent inclusive for a followup period ranging from 1 to 4½ years.

Finally, it should be mentioned that Mersilene® mesh or other synthetic materials should not be used indiscriminately as a panacea for the "simple problem" of hernia. However, there are specific indications, as have been mentioned previously, in which the use of such mesh can result in a sound repair without any appreciable increase in the rate of complication.

Conclusions

In an experimental study in which Mersilene® mesh was tested against simple suture closure of abdominal wounds in rats, the wounds of the group treated with the mesh exhibited significantly greater ($P < 0.01$) bursting strengths throughout the postoperative period.

Results of a clinical trial using Mersilene® mesh as an adjunct to the repair of hernia reveal a low rate of complication (1%) and a low rate of recurrence (1%).

Acknowledgment

We wish to express our appreciation to the Veterans Administration Hospital, New Orleans, Louisiana, for the use of its Surgical Research Laboratory where measurements of bursting strength were done. We also wish to express our appreciation to Touro Infirmary, New Orleans, Louisiana, for its generous financial support of the experimental study.

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DISCUSSION

DR. ARLIE R. MANSBERGER, JR. (Augusta, Georgia): I rise not because I have a wide experience with respect to the use of synthetic materials, but, rather, have had the opportunity to study five patients who had massive abdominal wall defects, in which we utilized combinations of synthetic materials in timed sequence for repair. Three patients had abdominal wall defects to include peritoneum resulting from massive necrotizing infections, one was the result of trauma, and a third was secondary to resection of a tumor of the colon growing into the anterior abdominal wall.

(A motion picture was started.) The proposed technique shown here utilizes a combination of accepted surgical principles and techniques and is carried out in logical sequences as follows:

1. Repair of peritoneal defects with Silastic sheeting. Sterile wet dressings with physiologic solutions applied over the sheeting to minimize postoperative fluid loss until an endogenous (fibromesothelial membrane) forms beneath it.

2. Removal of the Silastic sheeting in 3-4 weeks of coverage of the endogenous membrane with full-thickness skin and subcutaneous tissue flaps to enhance sterilization of the granulation tissue.

3. Elevation of full-thickness flaps and repair of fascial defect with Marlex mesh. (This procedure carried out 6 to 8 weeks following successful skin coverage.)

It is interesting to note that in the experimental animal adhesions do not occur on the undersurface of the endogenous membrane which forms deep to the Silastic sheeting.

I would like to ask Dr. Cerise if he has used Mersilene in the repair of large, full thickness defects.

DR. M. BERT MYERS (New Orleans, Louisiana): I don't think that the mesh used by Dr. Cerise actually altered the biology of wound healing, as the fascial autograft in Dr. Peacock's work did. I think it merely acts as a mechanical support, much the way sutures do. Therefore, the type of mesh becomes important.

(Slide) Two meshes are available on the market; the mersilene mesh, which Dr. Cerise used, is made of Dacron, and the marlex mesh, which is polypropylene. We recently ran a series of rats using the marlex mesh, and found results very similar to Dr. Cerise. At three days, the wounds supported by marlex mesh were at least three times as strong as controls, whereas after a week all of the wounds were of equal strength. The difference, however, is in the mesh itself.

(Slide) This is a photomicrograph of the mersilene mesh, showing how it's braided, which is an advantage in that when it is cut it doesn't unravel. A photomicrograph of the cut edge, however, shows that it is made of many small filaments, which is its one disadvantage. There are many places where bacteria can lurk in this mesh, which happened in one of Dr. Cerise's patients, and late infection would be expected if these wounds should get infected.

On the other hand, marlex is a monofilament knit. The knit type mesh keeps it from unraveling; but each filament is a single strand of polypropylene, so late infection should be much less likely with this material, and we have had hernias get infected and not remove the marlex and have them heal.

DR. ASHER R. MCCOMB (San Antonio, Texas): I arise to offer some remembrances of the past and present and to congratulate Dr. Cerise and his co-workers on this fine contribution.

It was my pleasure to have worked with the late Dr. John E. Cannaday, a deceased member, who was the first in this country to use cutis grafts. Drs. Otto Lowe and Edouard Rehn, German surgeons, were the first to advocate using cutis grafts in the World War I era. During my association with Dr. Cannaday, we used cutis to repair all types of hernias and defects of various sorts. This proved to be a very satisfac-

tory prosthesis, and, it was, we felt, the most satisfactory one available at that time.

Free fascial grafts, fascialata and various tissue transplants, such as the Bloodgood flap, are well known. The Bloodgood rectus fascia flap has been emphasized by another member, Dr. Rienhoff, Sr., and has been extensively used in inguinal hernia repair. We ran into hernias that were rather large to cover with fascia, and cutis graft has no limit as to how much you can take. It's always there. It cost nothing, except the time to cut the epidermis off and remove the cutis, and then use the epidermis to cover the defect.

While overseas during World War II, much appeared in the surgical literature about tantalum gauze mesh. On returning to practice it was discovered that Dr. Amos Koontz, a deceased member, had converted everyone to the use of tantalum, and I became a convert too. Then questions began to arise, such as, fragmentation of tantalum. Dr. Koontz, I remember, remarked, "Well it just acts as a form for fiberblasts to grow through, just like roses on a trellis. Actually, after a while the tantalum doesn't do anything but supply the form for formation of the scar which will hold the hernia intact."

Then along came a friend of mine from Houston, Dr. Francis Usher, who had developed and advocated marlex mesh. It was easier to handle than tantalum and was more appealing because of this. Later, the three of us were on a panel at a Texas State Medical Meeting. I was talked into using tantalum and marlex and haven't used cutis graft to any extent since then, but am seriously considering reverting to the use of cutis in selected cases.

In preparing a paper that was published in 1957 on cutis grafts, various and sundry materials that had been used and advocated as prosthesis in the repair of hernial defects were encountered in the literature. The number and variety of materials proposed was amazing.

We have encountered sad experiences with the use of both tantalum and marlex. I remember where tantalum was used in the repair of large epigastric hernias. The tantalum mesh fragmented and these patients came in several years later with abdominal abscesses which were felt due to perforation of the bowel by some of these fragments. These required drainage and later intestinal resection. Also, several complications occurred with marlex which supposedly were due to rejection phenomenon or allergy to this material since wound cultures were negative. One lady "spit" marlex fragments for nine years before clearing up. She was told that it wouldn't kill her. At the last A.S.C. meeting I saw a buttonhook contraption that I wished I had had to fish out some of these strands, because marlex is the devil to get out. We even went back in and tried to take some of this out, with little success.

It is to be recalled that Dr. Amos Koontz frequently stated, very emphatically, that he wouldn't do a hernia under general anesthesia. That a lot of hernias recurred in the recovery room fighting their way out of the anesthesia. We have all experienced this and one could almost see the sutures pulling out as the patient struggled with four recovery room attendants trying to hold him down. Perhaps we should find out preoperatively how these patients react to alcohol: whether they are "fighting drunks" or "crying drunks."

I prefer spinal anesthesia for herniorrhaphy, but it is difficult to get an anesthetist to administer spinal any more because of the medicolegal hazards. Recently I was impressed by Lichtenstein's work on repairing inguinal hernias under local anesthesia. Our friend and fellow member, Bill Lorimer, presented a paper before the Texas Surgical Society on the repair of a tremendous ventral hernia under local anesthesia. He gave several times the recommended dose of Lidocaine to repair this. The patient survived and made a good recovery. So I think that "peace and tranquility" of the abdominal wall enhances adequate healing. I would like to bring these few points to your attention.

I might add that, after cutis, full thickness skin graft was used. Later, objections were raised that cyst formation occurred. We did not experience this with cutis graft.

I have certainly enjoyed this paper and the opportunity to discuss it. I would like to hear what the essayists have to say about the use of cutis grafts.

DR. MONFORD D. CUSTER, JR. (Winchester, Virginia): In the fall of 1962 a patient was scheduled for surgery in the Winchester Memorial Hospital for repair, for the sixth time, of a very large abdominal incisional hernia. She was to be operated upon by Dr. Hugh Clark, one of the senior surgeons on our staff who, unfortunately, several days before the event, succumbed unexpectedly to a coronary attack. Somewhat to my dismay, I inherited this very nice lady as a patient.

I spent the first couple of days gleaning suggestions from anybody whom I could buttonhole for advice. I talked to Dr. Koontz, among a good many others, and I did get a lot of helpful suggestions, which I appreciated very much. But when I put it all together, I was still lost as to what to do.

What did help was a fine presentation by Dr. Joe Hamilton of his experience with 24 cases of onlay fascia lata grafts. I was very impressed, and a few days later employed this technique very successfully, and the patient remains well to date. We have used the operation 42 or 43 times. I certainly lend my modest endorsement to the insertion of this type of fascia as prosthetic material.

Now, Dr. Asher McComb has referred to cutis grafts. I can tell you about these too, because on one occasion I found it my responsibility to plan a reconstruction of not only the abdominal wall, but of the overlying skin devitalized as the result of a series of repair procedures.

It occurred to me, thinking once again that I was on the verge of world fame, that a composite graft of fascia lata and split thickness skin might serve the purpose. And it did. As a matter of fact, it was beautiful, at least while it lasted. Forty-eight hours later—well, I'm not going to tell you what happened to both components of the graft. I'll simply let you use your imagination. Anyway, although not fully recommending the composite type of graft, I certainly do endorse the principle of using fascia lata as prosthetic material. I have found it very satisfactory indeed. Thank you so much.

DR. COLIN G. THOMAS JR. (Chapel Hill, North Carolina) I rise to compliment the authors on their presentation, and also their excellent results. I think, however, many of us would prefer to use fascia lata for reinforcement.

There is a unique problem that arises in the child with gastroschisis or omphalocele. There may not be enough adjacent fascia for reconstruction and I should like to illustrate with one patient. This is an individual who had a large omphalocele which was repaired with skin flaps at the time of birth. We saw the child at the age of one and a half with a large ventral hernia occupying most of the upper abdomen. It was impossible in this patient to repair this defect with fascia lata. Instead we elected to mobilize the overlying skin and replace this area with marlex, recognizing

that it is undesirable to place the marlex in direct contact with the bowel. However, there being no omentum there was little alternative.

The immediate result was a reasonable one. About three years later, however, a small jejunal fistula developed. We observed this for another two years without it changing very much and then carried out a local excision of the fistulous tract, closed the bowel and repaired the marlex mesh. The ultimate result is that 10 years later there is an intact abdominal wall with good contour, no fistula and no hernia.

In general, with the other children we have seen we have used the approach that Dr. Peacock has emphasized; namely, employing fascia lata and also imbricating Scarpa's fascia.

I have one question for the essayists: Either in an experimental animal or in man have they had their mersilene mesh in direct contact with the bowel? If so, have they observed any ill effects?

DR. RONALD W. BUSUTTIL (Closing discussion): First, Dr. Myers, we are really not surprised that you have obtained very similar results to ours with the use of the marlex mesh. As Dr. McComb mentioned, Dr. Francis Usher, of Houston, Texas, first reported his experience with the use of marlex mesh in 1960. Since that time he has had good success with the use of this mesh in the treatment of certain types of hernias.

We do recognize that since marlex mesh is a monofilament, it would have a theoretic advantage over the polyfilament meshes, such as mersilene, in that the former should be less prone to harbor infection. However, in our clinical trial our infection rate was only one percent, this occurring in a patient twenty months postoperatively.

Furthermore, in our experimental model, mesh treated animals did not exhibit a greater infection rate. In fact, we have one group of rats which now have the mersilene mesh implanted for over eleven months without any untoward effects.

Dr. Mansberger, we thank you for sharing with us that very interesting and informative account of the use of synthetic mesh in the reconstruction of a large abdominal wall defect. We have had some experience with the use of this mesh in the reconstruction of a chest wall defect after resection for tumor, with satisfying results.

We thank Dr. McComb and Dr. Custer for their observations on the use of cutis grafts and of fascia lata. No, we have not used cutis grafts at the present time.

Finally, Dr. Thomas, our mersilene mesh has not been in contact with the intestine, so we do not have any first hand information on the potential incidence of fistula formation.

In summary, I would like to mention that normal wound healing is a fibrocollagenous process which is dependent on an inflammatory component. Thus, a therapeutic modality which is able to stimulate this inflammatory component, and yet be well tolerated by the host, would be expected to suggest wound healing.

It is our opinion that the use of mersilene mesh in selected cases of difficult hernia is such a modality which can effect a low rate of hernia recurrence with a very acceptable rate of morbidity.

The Use of the TDMAC-Heparin Shunt in Replacement of the Descending Thoracic Aorta

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The use of a flexible polyvinyl tube bonded with tridodecylmethylammonium-heparin (Gott) as a temporary shunt during the resection of lesions of the descending thoracic aorta has proven a safe and simple means of providing adequate circulation to the abdominal viscera and spinal cord. This technique avoids the metabolic consequences of ischemia to the lower body, diminishes left ventricular afterload during aortic clamping, and obviates the requirement for systemic anticoagulation associated with pump bypass. Between September 1970 and October 1974, 24 patients have been operated using the TDMAC shunt. There were two deaths (9%) among the 22 patients undergoing elective resections. Two patients with acutely dissecting and ruptured aneurysms expired. Followup data has been obtained on all patients from one to 46 months postoperative. The ease with which the shunt is inserted and its adaptability to varied clinical and anatomic situations is stressed. We feel that the TDMAC-Heparin shunt provides the best method of circulatory support for elective operative procedures on the descending thoracic aorta.

THERE IS CONTROVERSY regarding the best method of maintaining circulation to the abdominal viscera and spinal cord during the resection of a diseased descending thoracic aorta. Indeed the requirement for any temporary shunting of blood flow to these structures is questioned by those recommending rapid resection and grafting of the thoracic aorta. Crawford et al., reporting on a series of patients handled in this fashion, record low morbidity and mortality statistics.⁴ However, with both laboratory and clinical evidence indicating that periods of aortic clamping beyond 30 minutes are associated with paresis of the lower extremities, renal insufficiency and left ventricular failure due to excessive afterload,^{2,7,14} it is generally conceded that consistently operating within such time limitations un-

necessarily stresses the surgeon and jeopardizes the patient.

Simple bypass techniques with temporary dacron grafts⁸ and tygon conduits¹⁰ without anticoagulation have been recommended. The ever-present possibility of intraluminal thrombus formation with embolization seems to represent an unnecessary risk. Other methods of temporary bypass include femoral vein to femoral artery connection with an interposed pump oxygenator,^{13,14} and left atrial to femoral artery bypass using only an interposed pump.^{1,3,5} Estimates of the flow which constitutes adequate abdominal visceral perfusion are variable.^{1,7} Furthermore, the major disadvantage of these techniques relates to required systemic heparinization and associated perioperative hemorrhage.² Although this has not been an apparent problem in the series presented by the proponents of such methods,^{1,3,5,14} postoperative hemorrhage using these techniques was a major factor in the excessive mortality in an earlier group of patients treated at our institution.¹¹

Since 1970 we have used polyvinyl chloride shunts coated with a quaternary ammonium-heparin complex to provide local anti-thrombogenicity during the resection of descending thoracic aortic aneurysms. An initial experience with 8 patients has been reported.¹¹ The purpose of this report is to record our results from 1970 to the present with the use of these temporary conduits in 24 patients undergoing aneurysmectomy.

Techniques

The shunts used in this series were designed by Valiathan et al.¹⁵ and consist of 85 cm polyvinyl tubes with a central internal diameter of 12.5 mm and tapered ends 9 mm in

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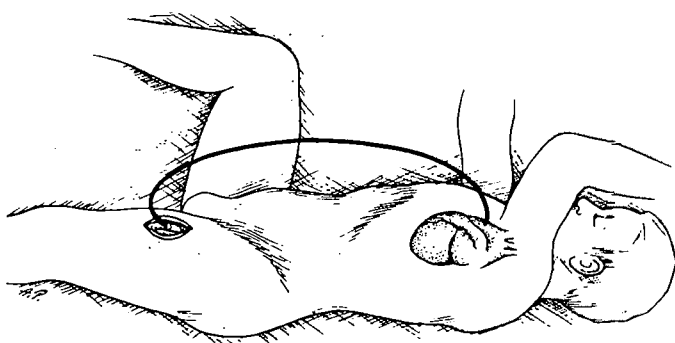


FIG. 1. Patient position with a functioning shunt.

diameter.* The tubes were sent to the Columbus (Ohio) Laboratories of Batelle Memorial Institute for coating with the tridodecylmethylammonium chloride (TDMAC)-Heparin complex and returned for gas sterilization (heat sterilization will destroy the heparin bond). Polyvinyl chloride collars (approximately 2 cm in length) are secured about the tubes with umbilical tapes 3 cm from each end. Immediately prior to use, 10 cc's of aqueous heparin (100

*Manufactured by Sherwood Medical Industries, 1833 Olive, St. Louis, Mo.

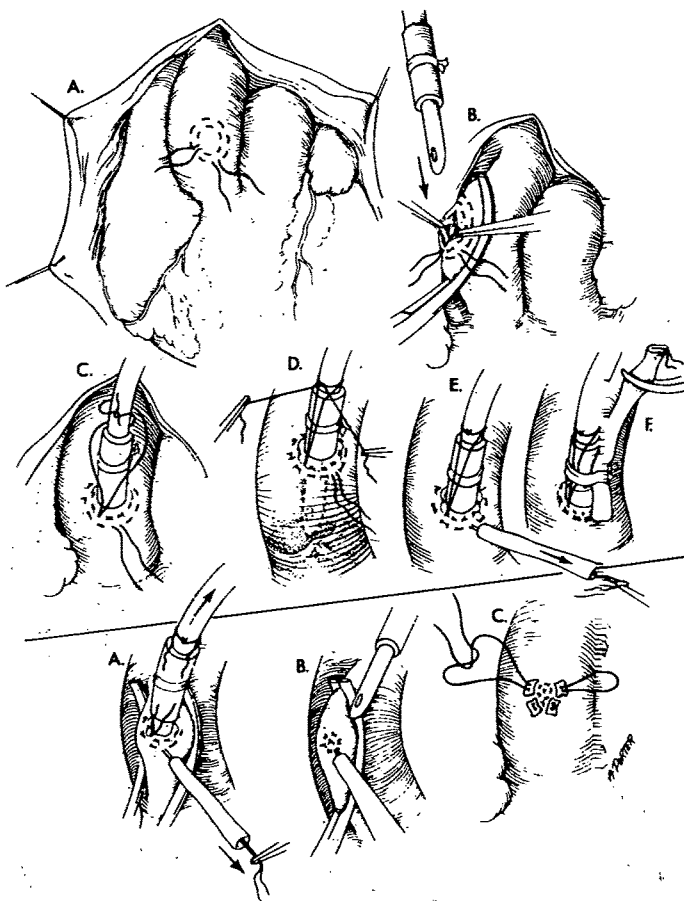


FIG. 2. Technique of aortic insertion (A-F); technique of aortic closure (G-I). Figs. 2 and 3 reproduced with the permission of Kratz, A. H., and associates, *Ann. Thorac. Surg.*, 14:2:123, 1972.

mgm) are mixed with 500 cc's of normal saline and the tubes are filled with this solution.

The patient is placed in the left thoracotomy position, with the right leg flexed to 90° and the left leg extended providing access to the left common femoral artery (Fig. 1). The left pleural space is entered through a left posterolateral thoracotomy incision with removal of the fourth rib. A lower interspace incision is sometimes performed through the same skin incision to allow exposure of the distal thoracic aorta. The aorta proximal and distal to the aneurysm is freed circumferentially and looped with tapes. Care is taken to avoid injury to the vagus and phrenic nerves.

The pericardium is then opened with a generous longitudinal incision anterior to the left phrenic nerve. A laparotomy pad is placed within the pericardium on the right side of the ascending aorta in order to elevate its left antero-lateral surface. The cannulation here is similar to that used in open heart procedures (Fig. 2). A double purse string suture of 2-0 Tevdek is inserted and a partial occlusion clamp applied. An aortotomy is carried out, the shunt inserted and secured with the inner purse string tied below and above the collar. The outer purse string is simply tightened through a rubber tourniquet and fastened about the mid point of the collar. The tube is clamped and not flushed until distal insertion is ready.

The common femoral artery is exposed and a segment isolated between vascular clamps (Fig. 3). A transverse arteriotomy is performed, the heparinized saline solution is flushed from the tube, and the distal end is carefully inserted to avoid sub-intimal dissection. A double ligature of heavy silk secures the distal end of the shunt with one of these ties again brought up over the collar. On occasion the

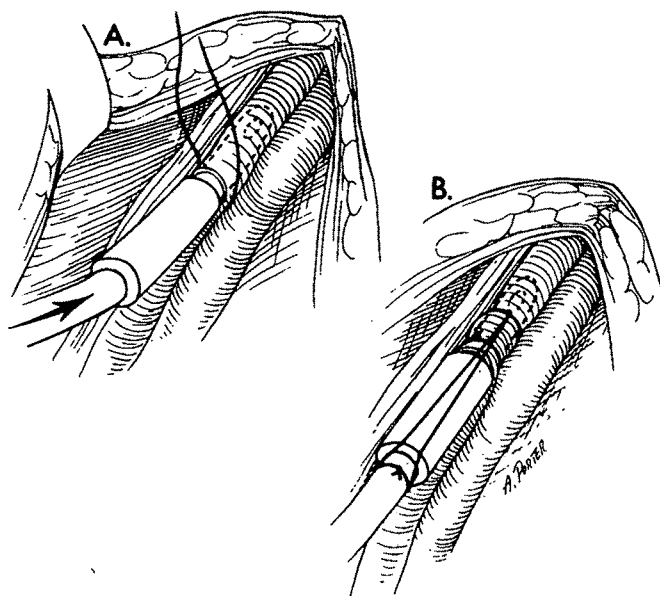


FIG. 3. Technique of common femoral artery insertion.

TABLE 1. *Types of Aneurysm and Results of Resection*

Patient	Age, Sex	Type of Aneurysm	Date of Surgery	Complication	Outcome	Cause of Death
R.W.	57, M	Ruptured	9/1/70		Died	Renal Failure
C.D.	60, F	Chronic dissection	9/14/70	none	Lived	
W.P.	65, M	Chronic traumatic	12/17/70	Re-operation for bleeding	Lived	
C.M.	54, F	Chronic dissection	12/31/70	none	Lived	
E.D.	70, F	Saccular (atherosclerotic)	1/29/71	none	Lived	
T.S.	61, M	Fusiform (atherosclerotic)	3/25/71	none	Lived	
H.H.	67, F	Chronic dissection	5/6/71	Acute tubular necrosis	Lived	
M.D.	75, M	Chronic dissection	6/2/71	none	Lived	
M.M.	56, M	Acute dissection	1/29/72	none	Lived	
G.A.	27, M	Chronic traumatic	3/28/72	none	Lived	
D.B.	72, M	Fusiform (atherosclerotic)	4/25/72	none	Lived	
W.W.	53, M	Chronic dissection	4/26/72	Re-operation for bleeding	Lived (paraplegia)	
E.G.	34, M	Acute traumatic	5/4/72	none	Lived	
G.R.	47, M	Saccular (atherosclerotic)	8/2/72	none	Lived	Cardiac arrest during surgery
N.S.	68, F	Ruptured	9/20/72		Died	
G.S.	71, M	Chronic dissection	10/2/72	none	Lived	
N.G.	57, F	Chronic dissection	12/12/72	none	Lived	
A.H.	46, M	Mycotic	5/27/73	Wound dehiscence	Lived	
C.S.	58, F	Fusiform (atherosclerotic)	9/20/73	none	Lived	
S.P.	71, F	Saccular (atherosclerotic)	10/30/73	none	Lived	Diffuse intravascular coagulopathy
S.M.	76, M	Fusiform (atherosclerotic)	12/14/73		Died	
S.H.	31, M	Chronic traumatic	2/18/74	none	Lived	
P.G.	71, M	Acute dissection	3/22/74	Ca lung Resp. Insuff. Acute tubular necrosis	Died	Myocardial infarction
W.B.	65, M	Saccular (atherosclerotic)	10/31/74	none	Lived	

common femoral vessel may be too small to accept the cannula tip. In such situations a short 10 mm woven dacron graft may be sutured to the arteriotomy and the shunt positioned within the graft. Clamps may be removed from the shunt at this point, and the bypass secured to the drapes anteriorly with umbilical tapes.

The diseased aortic segment is isolated with proximal and distal cross clamps. Patency of the shunt is confirmed by visible flow and evaluation of the pulsations or pressure measurements in the thoracic aorta. A woven dacron graft of appropriate diameter is pre-clotted. The lateral wall of the aneurysm is excised and bleeding intercostal vessels are suture ligated from within the aorta. If the distal false channel of a dissecting aneurysm cannot be totally excised, true and false channels are initially approximated and sutured to the distal graft. The anastomoses are carried out with running 3-0 Tevdek suture material. Debris and clot from the aortic lumen are flushed just prior to completion of the distal anastomosis. The distal clamp is removed first, with slow removal of the proximal clamp following. Patency of the shunt is maintained during this time so that hemorrhage at the anastomotic sites is minimized.

The shunt is clamped at the proximal end, the inner purse string is cut from the collar, and the tube withdrawn through a partial occlusion clamp on the ascending aorta. The outer

purse string is tied and the closure reinforced with 4-0 Tevdek mattress sutures over teflon felt pledgets. The tube is removed from the groin and the transverse arteriotomy repaired with fine vascular suture.

Radial artery cannulas on the right side monitor blood pressure continuously during the procedure and central venous pressure lines are likewise inserted. Prior to cross clamping the aorta, diuretics are given intravenously (usually Furosemide 80 mgm) to maintain urinary output during the aneurysmectomy. Blood gas values are determined frequently during the operation.

Results

Between September 1970 and October 1974, 24 patients with aneurysms of the descending thoracic aorta have undergone resection using the TDMAC shunt. There were 16 men and 8 women. Ages ranged from 27 to 76 years with an average of 58 years. There were 4 traumatic aneurysms, 11 aortic dissections, 8 atherosclerotic aneurysms and 1 mycotic aneurysm (Table 1).

Major postoperative complications included intrathoracic hemorrhage in two cases, necessitating reoperation for control. Two patients developed acute tubular necrosis with one requiring hemodialysis. This patient (H.H.) recovered completely and the other (P.G.) died 10

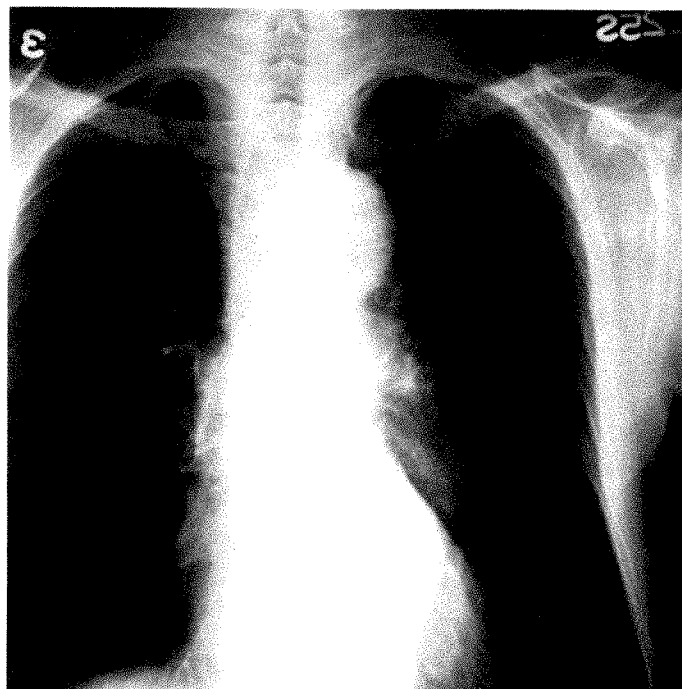


FIG. 4A. Admission chest x-ray (P.G.). Note widened aortic shadow and carcinoma right upper lobe.

days postoperatively of a suspected myocardial infarction. One patient (W.W.) who required reexploration 24 hours postoperatively for bleeding had good motor function in his lower extremities following the initial procedure. He developed paraplegia after his second operation which was probably related to the hemorrhage and inadequate collateral circulation to his spinal cord. A wound dehiscence occurred in another patient.

There were 4 operative deaths. Two patients had ruptured aneurysms but both survived long enough to have resections and graft replacements utilizing the Gott shunt. One died in the operating room following cardiac arrest and the other survived 4 days expiring with renal and hepatic failure. Among the 22 patients without evidence of rupture, there were 2 deaths. One patient died with massive hemorrhage and diffuse intravascular coagulopathy probably secondary to inadequate abdominal visceral perfusion. The left common iliac artery was severely stenosed with atherosclerotic disease in addition to which subintimal dissection had occurred. Flow in the shunt was present for a brief period following which it ceased completely and resection was completed with an extended period of visceral ischemia. The final fatality occurred in a 71-year-old man who entered the hospital with clinical and radiographic evidence of an acute dissection beginning distal to the left subclavian artery. In addition, plain chest x-rays revealed an infiltrative lesion in his right upper lobe and sputum cytologies were positive for epidermoid carcinoma. (Fig. 4). The patient was treated with antihypertensive agents; his symptoms diminished and his clinical situation

stabilized for several days. Radiation therapy to a right upper lung field was commenced, however, one month following admission, back pain redeveloped and a chest film showed considerable expansion of his aneurysm. An emergency resection was carried out; his postoperative course was marked by respiratory insufficiency requiring assisted ventilation with a tracheostomy, renal failure and sudden death on the tenth postoperative day due to a myocardial infarction.

Followup data are available on all 20 survivors through December 1, 1974 (Table 2). One patient (W.W.) died 5 months postoperatively with an acute myocardial infarction and multiple pulmonary emboli. A second patient (A.H.) had a fibroxanthosarcoma excised from his chest wall two years previously. He entered the hospital in May 1973 with shock and evidence of a massive left hemothorax. Emergency exploration revealed a ruptured metastasis involving the distal descending thoracic aorta. This was successfully resected; however he expired 11 months later with diffuse metastatic disease. The final late death (C.D.) occurred 23 months following surgery due to a probable myocardial infarction.

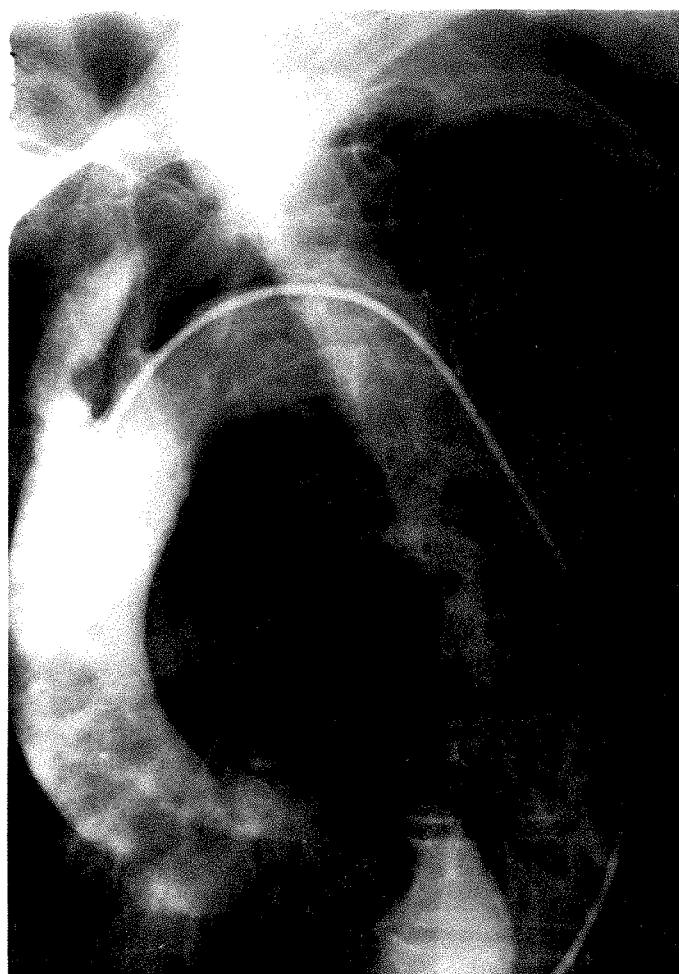


FIG. 4B. Aortogram (P.G.) shows extensive acute dissection.

TABLE 2. *Followup of TDMAC-Heparin Shunt Survivors (Through December 1, 1974)**

Patient	Date of Operation	Followup (Months)	Result
C.D.	9/14/70	23	Died 8/16/72—probable myocardial infarction
W.P.	12/16/70	47	Alive and well
C.M.	12/31/70	47	Alive and well
E.D.	1/26/71	46	Alive and well
T.S.	3/25/71	44	Alive and well
H.H.	5/23/71	42	Alive and well
M.P.	6/5/71	41	Alive and well
M.M.	1/29/72	34	Alive and well
D.B.	4/25/72	31	Alive and well
W.W.	4/27/72	5	Died 9/7/72—Recurrent pulmonary emboli and myocardial infarction
E.G.	5/3/72	30	Alive and well
G.R.	8/2/72	27	Alive and well
G.S.	9/25/72	25	Alive and well
N.G.	12/6/72	24	Alive and well
S.H.	2/19/73	21	Alive and well
G.A.	3/28/73	20	Alive and well
A.H.	5/29/73	11	Died with metastatic fibroxanthosarcoma
K.S.	9/20/73	13	Alive and well
S.P.	10/23/73	12	Alive and well
W.B.	10/31/74	1	Alive and well

*Average followup 27.2 months.

Comments

The morbidity and mortality associated with the resectional therapy of descending thoracic aortic aneurysms has markedly diminished in our institution since the initiation of temporary shunt bypass, without heparinization or pumping procedures. Resection techniques with or without hypothermia have the disadvantage of complete cessation of circulation to the abdominal viscera which too often exceed critical periods of time resulting in individual organ failure of poorly tolerated metabolic abnormalities in ill patients. Left atrial-femoral artery and femoral vein-femoral artery bypasses require systemic heparinization. These methods avoid aortic cannulation, diminish left ventricular strain and in the latter situation avoid conduits within the thoracotomy wound. Their profound disadvantage, however, is the need for systemic anticoagulation which too frequently results in uncontrollable hemorrhage from the graft, anastomosis, or mediastinum. The incidence of other complications such as renal failure and paraplegia are low, but nevertheless consistent in most series.^{1,4,9,13} The use of pump bypass is recommended in those patients suspected of having a ruptured aneurysm, since the insertion of femoral cannulas avoids mediastinal manipulation of the aorta and shed blood may be immediately recirculated.

The original non-thrombogenic surface developed by Whiffen et al.¹⁶ consisted of a graphite-benzalkonium-heparin complex which was dark and had a tendency to flake off when the tubes were clamped. The TDMAC-Heparin surface is transparent and allows visual estimation

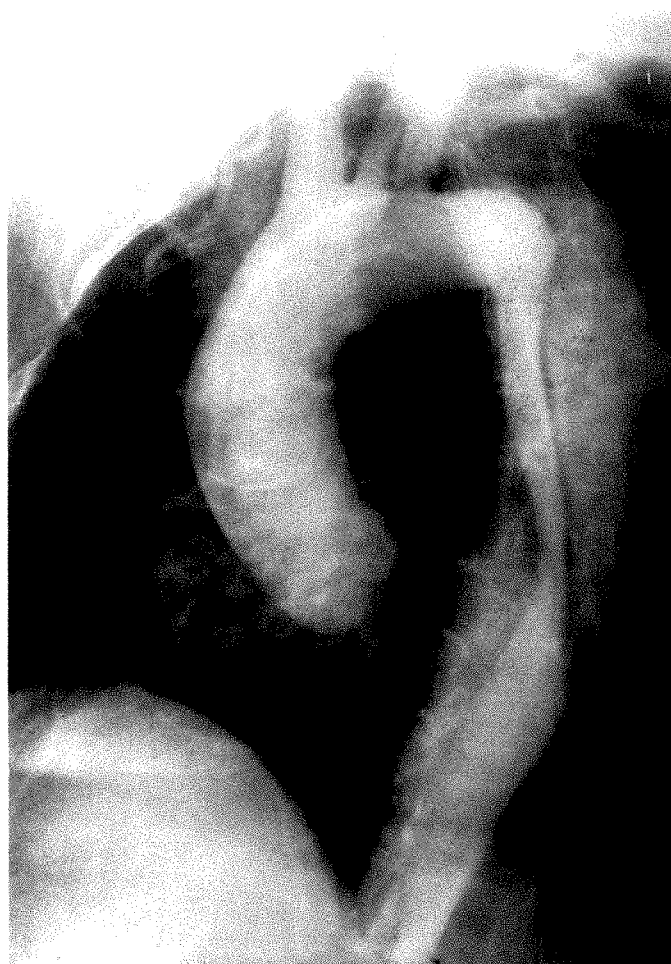


FIG. 5. Aortogram (K.S.), a 58-year-old Negro woman with a stabilized chronic dissecting aneurysm successfully resected 9/20/73.

of shunt flow. Furthermore, the heparin bond is very secure and the shelf life of a properly prepared tube indefinite. The long term effectiveness of this surface anticoagulant is attested to by Hagler et al. who have maintained dogs without systemic heparinization as long as 5 days on a partial veno-venous bypass with a membrane oxygenator and TDMAC-Heparin lined tubing.⁶ Mobin-Uddin recommends the insertion of TDMAC-Heparin coated cloth covered valvular prostheses and although the followup is brief (1-14 months) the incidence of thromboembolic problems is no greater than in a comparable group of patients treated with anticoagulants postoperatively.¹²

Several modifications in our technique of tube insertion have evolved. We now use the ascending aorta for the proximal cannulation. The left subclavian vessel is frequently too small in caliber to accept the cannula and the angulation in the apex of the chest is undesirable. The distal cannulation is performed in the common femoral artery although distal abdominal aorta and iliac vessels are acceptable. We rarely cannulate the distal descending thoracic aorta, since this presents kinking problems with

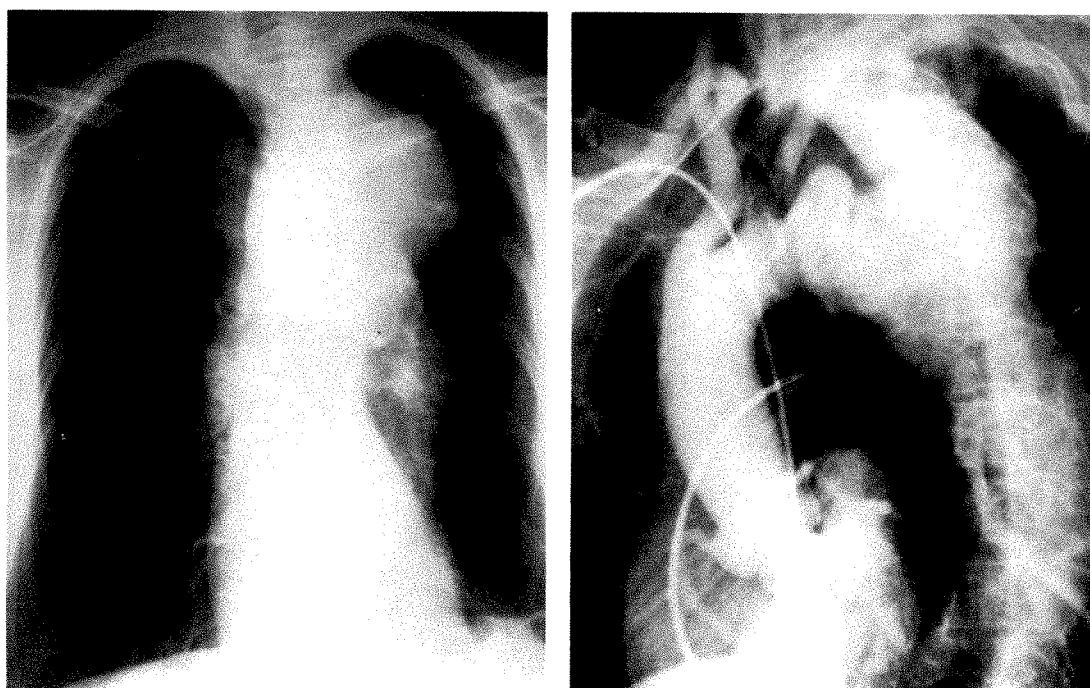


FIG. 6. Aortogram (C.D.), a 60-year-old Caucasian woman with a stabilized chronic dissecting aneurysm successfully resected 9/14/70.

the limited size of the polyvinyl tubes and decreases space available in the thoracotomy incision.

Blood gas measurements during and immediately following bypass reveal little or no metabolic acidosis. Urinary output has been satisfactory although two patients developed acute tubular necrosis postoperatively. One patient was dialyzed and recovered completely, the second patient died 10 days postoperatively probably due to a myocardial infarction. Paraplegia occurred in one case following a re-operation for hemorrhage. During the 24 hour period between the two procedures, motor function in his lower extremities was normal. Blood loss combined with marginal spinal cord collateral circulation were felt responsible for the development of this paresis.

In the 22 patients who underwent elective resection with no evidence of preoperative rupture, two expired (mortality 9%). The left common iliac artery was nearly occluded with atheromatous disease in one patient. His shunt functioned temporarily and with the addition of an intimal dissection prolonged abdominal visceral ischemia developed. He died with uncontrollable hemorrhage secondary to a diffuse intravascular coagulopathy syndrome. To avoid such disasters in the future, we routinely obtain aorto-iliac-femoral angiograms at the time of aortography and evaluate the patency of vessels proximal to the shunt. The second death in the elective group was in a very ill 71-year-old man with a carcinoma in his right upper lobe, chronic lung disease, and an acutely expanding dissection of the descending thoracic aorta. He died on the tenth postoperative day with a myocardial infarction.

In general, we have been satisfied with the visual and

palpable estimation of flow through the TDMAC shunts. Attempts to measure flow in the iliac vessels proximal to the shunt have not been reliable. We remain most interested in this parameter and further studies are planned in the future. Mean distal aortic pressures have been 55-60 mm Hg and with adequate urinary output combined with the absence of significant metabolic acidosis during bypass, flows appear clinically satisfactory.

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DISCUSSION

DR. GEORGE C. MORRIS, JR. (Houston, Texas): I do not think in the next several years we will see a resolution to the question of shunt versus no shunt. Any intervention in the descending thoracic aorta poses an inherent threat of ischemic cord injury, and considering the many relevant anatomical, pathological and physiological factors in this connection, some of us feel that the least important factor is aortic crossclamping.

Through the years since Denton Cooley of this organization performed the first aneurysm resection and reconstruction in this area, we have seen a number of memorable cases of paraplegia developing before operation, and, in other, days after successful operation, in association with hypotensive episodes. Furthermore, occasional patients have presented such severe technical problems that shunts were not used; and yet no cord defects ensued. Problems developing in other distal organs, such as the kidney and bowel have been related, in our experience, uniformly to mechanical situations with embolic debris and intimal dissection, rather than ischemia.

During the past six years, Stanley Crawford, Jim Howell and I have discontinued use of the shunts, and have achieved an operative mortality of 5%, and an incidence of cord injury less than 5% in over 120 elective cases.

(Slide) These are the figures from Stanley Crawford's personal series, and the major point I'd like to make in this series is that in the original group with shunts the operative mortality in the elective cases was 13%, with an overall mortality of 21%, and the incidence of some degree of cord injury was 3.3% in the elective group, and 7.9% in the total group.

In the more recent group of 59 patients without use of shunts, the elective mortality was 5%, and the incidence of cord injury was zero. I have had one patient with partial cord injury, who ended up with a foot drop. Jim Howell has had one paraplegic.

The points of particular importance to us in reducing mortality and avoiding problems with cord injury are: 1) avoidance of hypotension during and after operation; 2) preservation of collateral circulation by avoidance of extramural dissection around the aneurysm, in other words, leaving the aneurysmal adventitia and preserving the collaterals; 3) deflation of the left lung with a double-lumen endotracheal tube; and 4) avoidance of systemic heparin.

I know of a number of surgeons using the shunt now for one purpose only, and that is medicolegal. I think we have to approach our patients with

the same moral commitment that we operate on fellow physicians, and treat them as friends rather than potential plaintiffs.

DR. WALTER WOLFE (Durham, North Carolina): We have had very favorable experience at Duke with the shunt and the group at Duke approaches the problem much like Dr. Ferguson describes. We do feel there are other alternatives for cannulation. We have used the aorta, as described. We like to use the subclavian, if possible, and very recently in an acute transection Dr. Glenn Young, of the Association here, managed it by cannulating the apex of the ventricle to the femoral artery before manipulating hematoma.

We initially felt that the shunt was not indicated in acute, emergent situations, and, in fact, if you anticipate a great deal of shed blood, the pump oxygenator should be used to return the blood to the patient. However, Dr. Crawford, our Chief Resident, did successfully manage a gunshot wound of the thoracic aorta by using the shunt.

I would like to ask Dr. Ferguson to comment on some of the other contraindications, perhaps, to using the shunt. Early in our experience, I did have an unfavorable experience with a patient where there was aortic insufficiency associated with an atherosclerotic aneurysm; and perhaps where there is the problem or potential of increased afterload, the shunt should not be considered, and more standard cardiopulmonary bypass techniques used.

DR. THOMAS B. FERGUSON (Closing discussion): I certainly agree with Dr. Morris. They have a very impressive series. I don't believe a series of aneurysm resections done between 1955 and 1966 is strictly comparable to a recent series, but there is no doubt that if one has the technical facility to insert a graft rapidly that this removes one parameter of the total picture. In the community hospital, and for the surgeon who does not see a large number of aortic dissections, the shunt tube will be of great value. Certainly I agree with Dr. Morris that a medicolegal reason is a poor reason to select one technique over another.

Dr. Wolfe, I'm familiar with the experience in Durham. Cannulation of the apex of the heart is an alternate method which apparently works quite well. I would not use the shunt in a patient with free aortic regurgitation. That is asking the left ventricle to work too much.

I would stress the versatility of this shunt tube. I am sure it is adaptable for use in many other areas of surgery besides descending thoracic aortic aneurysms.

Resection of the Ascending Aorta Using Profound Local Hypothermia for Myocardial Protection

RICHARD H. BLANK, M.D., DENNIS F. PUPELLO, M.D., RICHARD G. CONNAR, M.D., LUIS N. BESSONE, M.D.

Resection of the ascending aorta with or without aortic valve replacement requires prolonged interruption of myocardial blood flow. Profound local cardiac hypothermia was used in 8 patients, 5 of whom had simultaneous aortic valve replacement. Three patients with acute dissections were encountered, one with cardiac tamponade secondary to intrapericardial rupture. The duration of aortic cross-clamp time varied from 43 to 122 minutes. There were no complications related to the cooling technique. There were no operative or hospital deaths. One patient died of myocardial infarction at 6 weeks. These results coupled with the experience of others suggest that coronary perfusion during periods of obligatory anoxia is unnecessary. Local cardiac hypothermia offers a satisfactory alternative for myocardial protection during prolonged aortic crossclamping.

INTERRUPTION of normal coronary perfusion is a prerequisite for resection of the ascending aorta with or without aortic valve replacement. Either anoxic arrest^{9,23} or artificial coronary perfusion has been the technique of myocardial protection used by most.^{3,6,13,16,17,20,26,28} We have used, instead, local deep hypothermia combined with a low perfusion rate in resecting aneurysms at this level. An unobstructed view of the aortic valve is provided facilitating its replacement or resuspension if necessary. Bypass time is shortened²² and injuries to the coronary ostia are avoided.²⁷

Local cooling of the heart was described by Shumway,²⁸ Hufnagel,¹⁸ and Urschel³⁰ over 10 years ago, but has not received wide acceptance. Through this presentation we would like to present our experience with local cardiac cooling and its safe application for extended operations on the aortic root. In addition, felt bolstering of the pericoronary aorta is used, thereby avoiding the necessity of reimplantation of the coronary arteries as has been recently recommended.^{31,29,17,4,10}

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Clinical Material

At Tampa General Hospital during the period from May 1973 through June 1974, 8 patients had resection of the ascending aorta. Two had graft replacement with aortic valve suspension only, while the remainder had graft replacement with insertion of a Bjork-Shiley prosthesis (5 patients) or valvuloplasty (1 patient). One patient (Case 2) had concomitant mitral valve replacement. Three had acute aortic dissections; two of these were limited to the ascending aorta (DeBakey Type II), while the third had a complete dissection beginning just above the aortic valve and extending to the abdominal aortic bifurcation (DeBakey Type I). Only one patient (Case 7) had the clinical features of Marfan's syndrome. All patients had an arch aortogram with or without cardiac catheterization. Aortic insufficiency and left ventricular enlargement were present in all cases. Table 1 and Table 2 summarize the pertinent findings and operative procedures. Two of the patients with acute dissections (Case 1 and 3) did not require valve replacement in that approximation of the dissected proximal aorta provided adequate suspension of the valve leaflets. One of these (Case 3) presented with a 24 hour history of excruciating back pain. The rapid development of neck vein distention and loss of her right femoral pulse prompted the performance of an arch aortogram. During the study she became hypotensive and was taken to the operating room and explored with minimal preparation. The pericardium was distended with fresh blood and its release produced a prompt improvement in cardiac output.

Rapid bypass was established by inserting the coronary

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TABLE 1. *Clinical Findings*

Case	Age-Sex	Symptoms	Cardiac Catheterization Data*
1.	63-M	Chest Pain	Type II Aortic Dissection
		Dyspnea	AI
2.	64-F	Dyspnea	Type II Aortic Dissection
			AI, AS, MI
3.	67-F	Back Pain	Type I Aortic Dissection
			AI
4.	48-F	Dyspnea	Fusiform Aneurysm
			AI
5.	68-F	Dyspnea	Fusiform Aneurysm
			AI
6.	56-F	Chest Pain	Fusiform Aneurysm
		Dyspnea	AI
7.	39-M	Dyspnea	Fusiform Aneurysm
			AI
8.	74-F	Dyspnea	Fusiform Aneurysm
			AI

*KEY: AI—Aortic Insufficiency; AS—Aortic Stenosis; MI—Mitral Insufficiency.

suckers into the right atrium through the amputated appendage and cannulating the femoral artery. Once a stable perfusion was achieved, individual superior and inferior caval catheters were inserted and the procedure conducted as outlined below.

Operative Technique

All patients were operated upon through a midline sternotomy employing a disposable bubble oxygenator*

*Temptrol, Bentley Laboratories, Inc., Irving, Calif.

primed with a liter of Ringer's lactate and 500 cc of heparinized blood. Standard cannulation techniques were used, achieving flow rates of 35-50 cc/kg/min, with perfusion pressure maintained between 50 mm and 70 mm/Hg. The edges of the pericardium were sutured to the anterior chest wall forming a receptacle for the cooling solution. Once stable bypass was established, the heart was fibrillated and the aorta cross-clamped just proximal to the innominate artery. The pericardial sac was then filled with normal saline cooled to 3C. The aorta was opened transversely to allow assessment of the valve. If replacement was warranted the valve leaflets were resected and the ventricular cavity irrigated with cold solution. A continuous infusion of cold saline, (30-50 cc/min), assured a constant low temperature in the pericardial well. A #12 plastic catheter was sutured to the left side of the pericardium for this purpose (Fig. 1), insuring that the dependent left ventricle was constantly immersed in the cold solution; the excess fluid was aspirated with wall suction. Tip sensitive thermistor probes were used in selected cases to monitor the temperatures in the right ventricular cavity, ventricular septum and epicardial surface (Fig. 2). A Bjork-Shiley prosthesis was used to replace the aortic valve in 5 patients following resection of the aortic leaflets. In two patients simple closure of a proximal dissection reinforced with a Teflon bolster restored valve competency. In the remaining patient, valvuloplasty was performed, consisting of elevation and suspension of the commissure between the right and noncoronary cusp. Upon completion of the valve procedure, a portion of the aneurysm was

CASE	OPERATION†	DATE	AORTIC X-CLAMP TIME	POST-OP COMPLICATIONS	FOLLOW-UP
1.	GRAFT ATA/25MM	5/19/73	62 MINS.	ATELECTASIS	DEATH 6/28/73
2.	GRAFT ATA/30MM AVR/B-S/21MM MVR/B-S/27MM	1/ 8/74	122 MINS.	RESP. INSUFF; LOW CARDIAC OUTPUT	LIVING 10 MONTHS
3.	GRAFT ATA/30MM	11/22/73	64 MINS.	RESP. INSUFF. LOW CARDIAC OUTPUT TRACHEAL STENOSIS	LIVING 12 MONTHS
4.	GRAFT ATA/35MM AVR/B-S/25MM	7/17/73	62 MINS.	NONE	LIVING 16 MONTHS
5.	GRAFT ATA/30MM AVR/B-S/23MM	1/22/74	66 MINS.	NONE	LIVING 10 MONTHS
6.	GRAFT ATA/30MM AVR/B-S/23MM	2/19/74	57 MINS.	NONE	LIVING 9 MONTHS
7.	GRAFT ATA/35MM AVR/B-S/29MM	5/ 9/74	97 MINS.	NONE	LIVING 6 MONTHS
8.	GRAFT ATA/35MM AORTIC VALVULOPLASTY	6/24/74	43 MINS.	NONE	LIVING 5 MONTHS

TABLE 2. *Operative Results*

† KEY:

ATA - ASCENDING THORACIC AORTA
AVR - AORTIC VALVE REPLACEMENT
MVR - MITRAL VALVE REPLACEMENT
B-S - BJORK-SHILEY PROSTHESIS



FIG. 1. Cross sectional view showing level of cold saline maintained by continuous flow through a #12 plastic catheter sutured to the left side of the pericardial well. A constant level is maintained by use of wall suction shown on right side.

excised leaving the posterior wall intact, thereby avoiding possible injury to the underlying pulmonary artery. Care was taken to leave a sufficient rim of aorta surrounding the

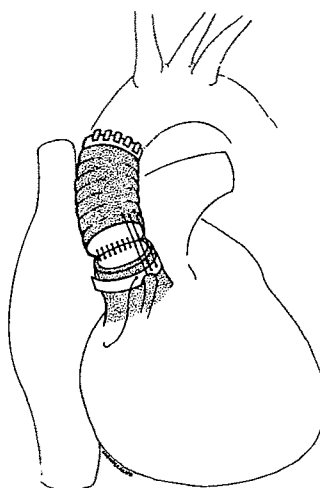


FIG. 3. Simple method of incorporating strips of teflon felt on the aortic side of the anastomosis. For illustrative purposes the distal suture line is shown completed.

coronary ostia so that luminal compromise was avoided during placement of the proximal suture line. A woven dacron prosthesis was selected and its proximal end cut with appropriate obliquity to compensate for the usual discrepancy in the proximal and distal aortic lumens. A 1.5 cm wide Teflon felt bolster was incorporated in the suture line (Fig. 3), providing needed reinforcement to the weakened aortic wall. The proximal aortic suture line was completed first, allowing more accurate placement of the posterior sutures at this level. The distal suture line was then inserted as systemic rewarming began. All air was aspirated from the ascending aorta and the cross-clamp removed. Once the esophageal temperature reached 35°C and adequate ventricular fibrillatory activity appeared, the heart was defibrillated, followed by gradual discontinuance of bypass.

Results

Aortic cross-clamp times ranged from 62 to 122 minutes, with an average of 72 minutes (Fig. 4). There were no operative or hospital deaths. One patient (Case 1) died 6 weeks postoperatively from a myocardial infarction proven at autopsy. The surviving patients are all significantly improved. Aortic insufficiency has not been detected clinically in any of the survivors. Three patients had significant postoperative complications. Two required prolonged ventilatory support for respiratory insufficiency, with the development of mild tracheal stenosis in one (Case 3). The other patient (Case 1) had persistent atelectasis requiring several bronchoscopies for resolution. There were no instances of postoperative hemorrhage, but inotropic support was necessary for more than 24 hours in the two patients with respiratory insufficiency. Microscopic evidence of cystic medial necrosis was found in all cases.

Discussion

Syphilis, giant cell aortitis,² and arteriosclerosis⁹ are occasional causes of aneurysms of the ascending aorta. The

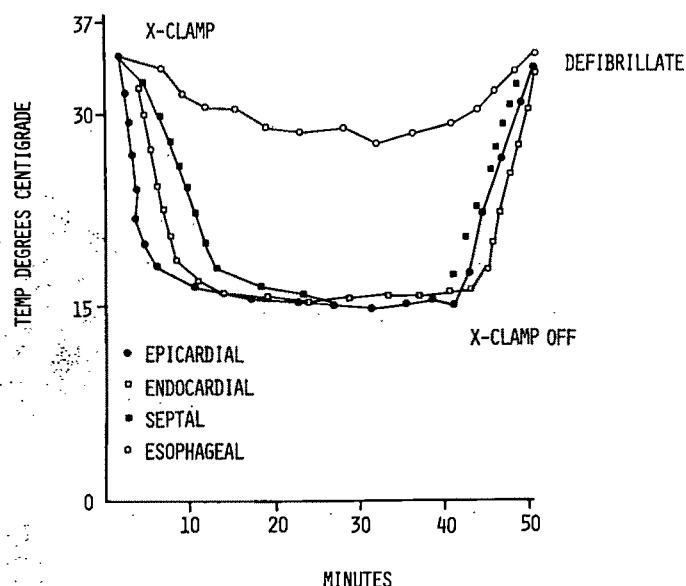


FIG. 2. Temperature readings from representative patient showing rate of fall at different sites. Note that septal temperature required approximately 12 minutes to reach 15°C. Cooling is begun simultaneously with aortic cross-clamping. Endocardial temperature is measured in the right ventricle.

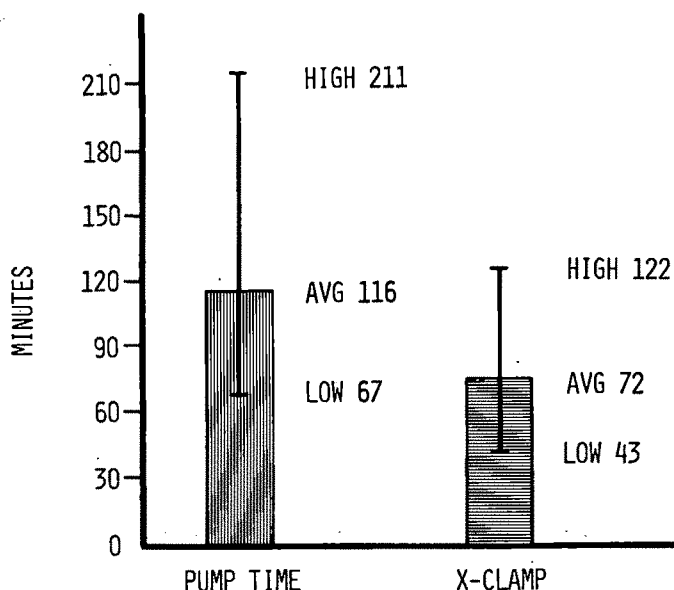


FIG. 4. Graphic display of total pump and aortic cross-clamp times.

majority, however, are secondary to cystic medial necrosis, which may or may not be accompanied by the skeletal stigma of Marfan's syndrome. The basic defect is considered to be a form of abiotrophy, in that the elastic tissue within the aortic media deteriorates prematurely.²⁴ Disruption and disappearance of the elastic fibers associated with hypertrophy and disorganization of the adjacent smooth muscle are the histological features.²⁴ While the basic disorder is generalized, the ascending aorta is most often affected by either fusiform aneurysmal dilatation or intermedial dissection. This predilection is explained by the fact that the ejectile force of the left ventricle is maximal in the first portion of the aorta diminishing progressively along the course of the vessel.²⁴ The suggestion that the entire ascending aorta should be resected down to the aortic annulus^{4,10,17,29,31} is based on the supposition that recurrent aneurysm formation in the residual aorta might compromise long term survival. Reports of such occurrences are notably lacking in the literature. The use of synthetic felt to reinforce the thinned out proximal aorta was first suggested by Hufnagel.¹⁹ A subsequent report by Gerbode,¹³ has established the principle of buttressing the aortic side of the suture line to prevent excessive bleeding and subsequent aneurysm formation. The need to remove all aortic tissue, thus necessitating reimplantation of the coronary arteries is not warranted except in instances of gross distortion of the annular-coronary ostia spatial relationships.

Myocardial protection during periods of obligatory interruption of coronary flow has been provided by individual coronary artery perfusion in most reported instances of ascending aortic resection.^{3,6,13,16,17,20,26,28} Nor-

mothermic anoxic arrest has been used extensively by Cooley's group^{9,23} and is a technique that provides a relatively bloodless field, unencumbered by the presence of cannulas and bothersome coronary sinus return. Problems with low output syndrome and "stone heart" have dampened some of the early enthusiasm for this method.¹⁴

The heart, while considered a sturdy organ as far as its ability to tolerate interruption of its blood supply, may show significant histological and enzyme changes following relatively brief periods of ischemia.^{5,11,12} The lack of myocardial oxygen reserve is reflected in the constant high arteriovenous gradient of coronary blood regardless of cardiac activity. With cessation of coronary flow the production of high energy phosphate bonds necessary for maintenance of transmembrane gradients must be achieved through anaerobic pathways.²⁵ With the loss of oxidative phosphorylation the efficiency of energy production is reduced to 5% of normal.²⁵ Removal of the ventricular afterload by aortic cross-clamping reduces energy requirements, but even in the non-beating heart continued production of high energy phosphate bonds is mandatory if intracellular electrolyte concentrations are to be preserved. A method of quantitating the stage at which anaerobic metabolism becomes inadequate for the necessary energy production in the ischemic myocardium has been reported by MacGregor.²⁵ He has shown that the safe period of anoxic arrest is related to the individual metabolic activity rather than to a specific time interval. While significant enzyme depletion and demonstrable changes in the myocardial ultrastructure occurring during longer periods of myocardial ischemia may still permit survival, the effect such injury may have over long periods of time has not been clearly defined.^{5,14} Systemic or local induced hypothermia in the 10-12°C range lowers the metabolic demands of the myocardium tenfold.¹⁵ Angell¹ has shown that the duration of allowable anoxia is a linear function of the logarithm of temperature making viability of the heart predictable if anoxia times and temperatures are known. The technique of simple surface cooling as a means of providing adequate myocardial protection has been questioned by some.³⁰ Using moderate systemic hypothermia coupled with the application of cold normal saline (3°C) to the heart after cross-clamping will produce a drop in the myocardial temperature to 12-15°C in a period of 10-12 minutes.²⁸ Urschel and Bjork suggested perfusion of the coronary arteries with cold blood to achieve a faster temperature drop as well as providing an even distribution of the cooling solution throughout the myocardium, thereby avoiding significant temperature gradients.^{6,30} While results of animal studies⁷ would lend credence to this concept, clinical results¹⁵ suggest that this addition is not necessary. All agree,^{1,12,15,19} however, that once cooling has been achieved by topical methods, it is imperative that the tendency for rewarming be avoided. We feel that systemic hypothermia combined with low flow rates are

important in this regard. The time limit of one hour for myocardial ischemia using this method as suggested by Robiscek²⁷ is probably too conservative, since recovery has been reported in a number of cases^{8,15,21} in which aortic cross-clamp times have exceeded two hours.

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DISCUSSION

DR. WATTS R. WEBB (Syracuse, New York): I rise primarily because I think any excellent paper like this deserves discussion and commendation for the author for the very excellent work that he has presented.

I will say that we follow very much the same rules of technique and procedure. We happen to use the lactated Ringer's slush, rather than the continuous intrapericardial administration of cold saline, but it achieves essentially the same thing, with an excellent degree of hypothermia, and the usual time limits of two hours are certainly extremely well tolerated with this procedure.

As you know, our work and that of Dr. Shumway demonstrated many years ago that at least experimental hearts at 4°C could go up to seven and eight hours and be reimplanted and work perfectly well.

We do use one other refinement of this technique and that is, at the start after crossclamping the aorta we introduce a large needle into the ascending aorta and infuse up to a liter of chilled lactated Ringer's, which will be at 3 or 4°C. This gives cooling of the entire myocardium down to about 10°C. immediately, rather than having to wait some 12–15 minutes to achieve this with either external or intracavitary perfusion, since the coronary flow gives very rapid, immediate cooling of the entire myocar-

dium. The heart, of course, stops very quickly at this cold temperature, which is fine. One may have to manually massage the heart a little bit during the continuation of the perfusion into the ascending aorta.

The other difference is that we try awfully hard not to operate on any of these dissecting aneurysms acutely, and will use extreme medical management in order to tide them over for two to three weeks. At this time the acute edema has subsided, the tissues are much better and operation much easier.

DR. RICHARD H. BLANK (Closing discussion): Thank you, Dr. Webb, for your comments. I too feel that infusion of cold solution into the clamped aorta certainly does speed up cooling.

(Slide) Dr. Pupello, who has been primarily responsible for this work, reported our experience with aortic valve replacements using the same technique. The clinical results thus far in a group that now totals 94 patients, including two triple-valve replacements, has been accomplished without an operative or hospital death. So at present we are going to continue using this method as described.

Our concern is that survival alone does not necessarily mean that there has not been some myocardial injury and perhaps some time in the future we may adopt the technique of perfusing the proximal clamped aorta to hasten myocardial cooling.

Membrane vs Bubble Oxygenator: Clinical Comparison

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DONALD H. GLAESER, D.Sc., MICHAEL E. DEBAKEY, M.D.

Numerous studies have demonstrated the superiority of membrane oxygenators (MO) over the bubble oxygenators (BO) when used for prolonged cardiopulmonary support. However, there is little information available evaluating the MO for routine, short-term cardiopulmonary bypass. In this study the 5M0314 Modulung-Teflo[®] (MO) was compared to the 5M30314 Mini-prime Variflo[®] (BO). The data of 91 patients (46 MO and 45 BO) were analyzed according to the duration of cardiopulmonary bypass (Group I < 60 min., Group II 60-90 min. and Group III > 90 min.). Hemodynamic parameters, fluid and blood balance, as well as hematologic and blood gas studies were used for comparing the two oxygenators. The hemodynamic parameters were better, and the arterial blood gases were more physiologic with the MO. The postoperative blood loss was significantly less when using the MO. The other measurements documented the stability of the MO. All statements were based on statistical analysis with a DEC[®] PDP-9 computer, using the MHS[®] language and operating system. Consequently, we are now using this MO for routine cardiopulmonary bypass.

SINCE the pioneering efforts of Gibbon⁷ nearly forty years ago, numerous devices have been developed to oxygenate the blood in an extracorporeal circuit. The multitude of oxygenators which have been introduced indicates incomplete satisfaction with any one particular mode of extracorporeal gas exchange. At present, the major unsolved problems include protein denaturation, blood trauma, coagulation defects and microembolization.^{1,3,5,10,11,15-17} Most of these complications have been

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considered to be secondary to the blood-gas interface of bubble oxygenators.^{11,12,14} Consequently, membrane oxygenators have been developed to eliminate this blood-gas interface. Although clinical application of membrane oxygenators has not alleviated all the aforementioned problems, they have been found to be superior for long-term extracorporeal oxygenation.^{3,9,14,18} More recently membrane oxygenators have been suggested for gas exchange during routine cardiopulmonary bypass procedures.^{4,8,13}

The purpose of this study was to compare the 5M0316 Modulung-Teflo[®]* disposable membrane oxygenator (MO) with the 5M0314 Mini-prime Variflo[®]* disposable bubble oxygenator (BO) during routine, short-term cardiopulmonary bypass for open heart surgery.

Clinical Material and Methods of Study

Analysis of data from 91 consecutive patients requiring cardiopulmonary bypass provides the basis for this study. There were 62 men and 29 women ranging in age from 20-82 (avg. 50.8) years. All patients were operated upon by the same surgical team. The procedures performed included aortocoronary artery bypass (53), valve replacement (30), correction of congenital heart defects

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*Travenol Laboratories, Inc., Artificial Organs Division, Morton Grove, Illinois, U.S.A.

TABLE 1. *Distribution of Patients According to the Duration of Cardiopulmonary Bypass and the Procedures Performed*

Group	Oxygenator	Total number of cases	Coronary Artery Bypass	Valve Replacement	Congenital Defects	Other
I <60 min.	BO	22	12	5	2	2
II 60-90 min.	MO	23	18	5		
	BO	15	8	5		2
III >90 min.	MO	16	8	7	1	1
	BO	8	6	2		
	MO	7	1	6		
Total number of cases		91	53	30	3	5

(3) and others (5). There were 45 patients operated upon using the BO while in the remaining 46 patients the MO was employed. To more precisely evaluate these two oxygenators, the patients were divided into three subgroups depending upon the duration of cardiopulmonary bypass: Group I <60 minutes, Group II 60-90 minutes and Group III >90 minutes (Table 1).

Cardiopulmonary bypass was established in all patients using caval cannulation through the right atrium and perfusion of the ascending aorta with a 20F aortic cannula.* Occlusive roller pumps were used with both oxygenators. Miniprime (5M0335) disposable heat exchangers and Swank** CA-100 extracorporeal filters were used in the cardiotomy return system of both circuits. With the BO the heat exchanger was placed into the venous line while with the MO the heat exchanger was placed between the oxygenator and the arterial reservoir. The same size perfusion tubings were used with both oxygenators; 13 mm tubing for the venous line, 9.5 mm for the pumphead portion and 6.4 mm for the arterial line. Both oxygenators were primed with 5% dextrose in lactated Ringer's (20 ml/kg body weight) containing 25 mg sodium heparin per liter. For both oxygenators 100% O₂ was used with a flow rate of 6-9 L/min for the BO and 10-12 L/min for the MO. In the MO dry oxygen was heated before entering the oxygenator, in order to prevent condensation of water vapor from the blood passing across the microporous membrane.

The Modulung-Teflo[®] oxygenator consists of an expanded fibrillated tetrafluoroethylene (Teflon[®]) membrane with an effective pore size of 3-5 microns contained within a rigid plastic case. The membrane itself is arranged in an accordion pleated fashion with 30 blood phase envelopes alternating with 30 gas phase envelopes. The actual surface area of the membrane is 2.25 M,² although the effective surface area for gas exchange is

somewhat less, due to supporting screens in both the blood and gas phases. The rigid front plate facing the blood phase envelopes contains the blood inlet and outlet ports, while the rigid back plate facing the gas phase envelopes contains the oxygen inlet and outlet ports. Through the rigid back plate passes a tube connected to an inflatable "shim" bag contained within the middle of the stack of envelopes, so that inflation of the "shim" bag decreases thickness of the blood phase envelopes. Oxygen transfer rate is increased by increasing the "shim" pressure, which decreases thickness of blood phase envelopes, and by increasing recirculation. It can be decreased by lowering the "shim" pressure and by decreasing recirculation. Carbon dioxide transfer rate is controlled primarily by oxygen flow rate, an increase in oxygen flow increasing carbon dioxide elimination and a decrease in oxygen flow decreasing carbon dioxide elimination.

The various hematologic studies performed and the sampling times are listed in Table 2. The pump flow rates and mean arterial pressures also were compared. The quantity of urine produced during cardiopulmonary bypass and in the first 24 hours after operation was measured, as was the amount of blood lost into the thoracos-

TABLE 2. *Measured Parameters and Sample Times**

Hematologic Studies	Sample Time Cardiopulmonary Bypass				
	Preop	Pre-	Mid-	Post	Postop 24 hrs
Serum hemoglobin		x	x	x	x
Plasma hemoglobin	x				x
Prothrombin activity	x				x
Blood urea nitrogen	x				x
Serum creatinine	x				x
Arterial blood gases		x	x	x	

*United States Catheter and Instrument Corporation, A division of C. R. Bard, Inc., Box 566, Billerica, Mass. U.S.A.

**COBE Laboratories, Denver, Colorado U.S.A.

*Hemodynamic measurements = (Pump flow rates and blood pressure); Fluid and blood balance; urinary output; blood loss; blood transfusions.

TABLE 3. Significant Differences Using Modified *t*-Test

Variable (x)	Group	^a BO	^a MO	^t	^f	^a BO	^a MO	^{SD} BO	^{SD} MO
Mid Bypass PCO ₂	II	15	16	3.14	26	30.8	35.8	3.43	5.31
Mid Bypass PCO ₂	III	8	7	4.29	7	28	35.9	1.51	4.63
Pump Flow Rate	I	21	22	9.77	34	3571	5295	467	675
Perfusion Pressure	III	7	6	2.44	7	80.7	90.8	10.2	3.77

Note: *t* = the standard Student *t*-statistic; *f* = the calculated degree of freedom from equations 2 & 3; *x* = the sample mean of the variable; *SD* = sample standard deviation; *n* = number of members in the group population.

tomy bottles and transfusions required during this same period. Any postoperative pulmonary, renal or neurologic complications also were analyzed.

All data were entered into a disc file on a DEC® PDP-9 computer. Application programs were written in the Meditech Interpretive Information System® (MIIS) language. Thirty-seven measurements and 19 derived parameters were used to assess the differences between the two oxygenators in each of these groups. In most cases the derived data were averages computed over intervals (pre-bypass, during bypass and post-bypass), although data represented by single measurements were used in some comparisons. For example, comparison of *P*_{O₂}, *P*_{CO₂} and serum hemoglobin during bypass was performed by using the single sample nearest the middle of the bypass interval and also by the average of these data over the entire interval. Although the level of significance was occasionally different using single measurements and averages, the results were unaltered. Specifically, in Group II the difference in *P*_{O₂} at the mid-interval samples was significant at the *P* > 0.01 level, while the difference in average *P*_{CO₂} during cardiopulmonary bypass was significant at *P* > 0.05, but not at *P* > 0.01. The mean, Variance, range and *t*-statistic of each sub-population defined above was computed. For each bypass interval and each

data element, the variances of the BO and MO groups were tested for equality using Fishers *v*² test.⁶ If a significant difference was observed, a modified statistic defined by equation (1) was computed.

$$t^1 = \frac{\frac{x_1 - x_2}{s^2}}{\frac{1}{n_1} + \frac{1}{n_2}} \quad (1)$$

x_i = sample mean of group *i*

s_i² = sample variance of group *i*

n_i = number of members of group *i*

This statistic has been shown by Welch¹⁹ to be distributed approximately as "*t*" with *f* degrees of freedom, where *f* is determined from equations (2) and (3)

$$c = \frac{\frac{s_1^2}{n_1}}{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}} \quad (2) \quad \frac{1}{f} = \frac{c^2}{f_1} + \frac{(1-c)^2}{f_2} \quad (3)$$

The measurements which differed significantly (*P* > 0.05) using this modified test rather than the standard *t*-test are tabulated in Table 3. All other results were obtained from the standard *t*-test.

TABLE 4. Serum Hemoglobin Studies

Group	Oxygenator	Pre-Bypass			Mid-Bypass			Post-Bypass			24-hrs		
		SeHb	SD	P	SeHb	SD	P	SeHb	SD	P	SeHb	SD	P
I	BO	11.66	1.38	NS	9.07	1.07	NS	11.72	1.22	NS	11.61	1.59	NS
	MO	11.53	1.38		8.96	1.07		11.89	1.40		12.21	1.05	
II	BO	10.68	1.73	NS	8.85	1.12	NS	11.56	1.10	NS	11.48	1.23	NS
	MO	12.03	1.67		9.75	1.13		11.36	1.68		11.47	1.53	
III	BO	11.88	2.09	NS	9.65	1.84	NS	10.05	1.29	NS	10.65	0.96	NS
	MO	12.37	1.79		9.60	0.71		10.27	1.44		11.74	0.92	

Note: SeHb = mean serum hemoglobin value (g%); SD = standard deviation; P = level of significance; NS = non-significant.

TABLE 5. Plasma Hemoglobin Studies

Group	Oxygenator	Preop			24 Hrs Postop			Mean increase PIHb		
		PIHb	SD	P	PIHb	SD	P	PIHb	SD	P
I	BO	5.68	5.77	NS	15.50	17.19	NS	8.83	15.34	NS
	MO	6.42	8.14		10.44	8.51		4.0	5.75	
II	BO	5.07	2.99	NS	12.14	7.77	NS	6.33	6.62	NS
	MO	6.81	8.70		9.66	8.33		1.22	15.11	
III	BO	5.12	6.31	NS	19.50	22.65	NS	13.0	28.99	NS
	MO	4.16	1.72		15.38	18.28		9.2	18.19	

PIHb = mean plasma hemoglobin (mg%)

TABLE 6. Prothrombin Activity Studies

Group	Oxygenator	Preop			24 Hrs Postop		
		Proth	SD	P	Proth	SD	P
I	BO	12.49	0.73	NS	14.01	1.61	NS
	MO	12.13	0.65		13.21	0.91	
II	BO	12.38	1.04	NS	13.3	1.19	NS
	MO	12.11	0.85		13.52	1.67	
III	BO	12.00	0.77	NS	12.36	0.05	NS
	MO	12.71	0.78		12.96	0.89	

Proth = mean prothrombin activity (seconds).

TABLE 7. Serum Creatinine and Blood Urea Nitrogen Studies

Group	Oxygenator	Preop			24 Hrs Postop			Preop			24 Hrs Postop		
		SeC	SD	P	SeC	SD	P	BUN	SD	P	BUN	SD	P
I	BO	1.05	0.34	NS	1.08	0.34	NS	15.72	5.09	NS	13.68	5.56	NS
	MO	1.00	0.22		1.00	0.25		14.65	5.05		13.34	3.97	
II	BO	1.16	0.36	NS	1.42	0.58	NS	20	12.9	NS	22.33	14.81	NS
	MO	1.06	0.25		1.27	0.40		16.37	4.25		17.12	6.14	
III	BO	1.02	0.14	NS	1.45	0.75	NS	16.25	3.99	NS	15.87	6.03	NS
	MO	1.08	0.31		1.35	0.43		19.57	8.73		19.14	8.53	

SeC = mean serum creatinine (mg%)

BUN = mean blood urea nitrogen (mg%)

Results

Hematologic Studies

The results of the serum hemoglobin studies are shown in Table 4, which reveals non-significant differences between the BO and MO groups. Plasma hemoglobin studies also showed no significant differences (Table 5). The mean increase in plasma hemoglobin concentration at 24 hours was also not statistically significant in any group. Measurement of the prothrombin activity revealed no significant changes (Table 6). The effects of the two different oxygenators on renal function were evaluated using serum creatinine and blood urea nitrogen studies, and these also revealed no significant differences (Table 8).

The pre-, mid-, and immediate post-cardiopulmonary bypass arterial P_{O_2} and P_{CO_2} values are presented in Table 8 which shows adequate gas exchange in all groups. However, the mid-bypass P_{O_2} and P_{CO_2} were significantly closer to physiological ranges in all three groups using the MO.

Hemodynamic Measurements

Table 9 presents the pump flow rates, the perfusion pressures in the radial artery and the total urine output during cardiopulmonary bypass. The flow rates and perfusion pressures were significantly higher in all subgroups using the MO, despite the fact that average body weights were comparable. There were no significant dif-

TABLE 8. Blood Gas Studies

Group	Pre-Bypass						Mid-Bypass						Post-Bypass					
	I		II		III		I		II		III		I		II		III	
	BO	MO	BO	MO	BO	MO	BO	MO	BO	MO	BO	MO	BO	MO	BO	MO	BO	MO
Oxyg	268	254	235	242	247	225	448	319	457	313	443	269	229	218	211	244	232	228
P _{O₂}	132	101	109	106	136	100	100	89	81	99	73	88	85	82	92	110	89	11
SD	NS	NS	NS	NS	NS	NS	<0.001	<0.001	<0.001	<0.001	<0.002	<0.002	NS	NS	NS	NS	NS	NS
P	NS	NS	NS	NS	NS	NS	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	NS	NS	NS	NS	NS	NS
P _{CO₂}	38	37	38	39	35	41	30	35	30	35	28	35	38	39	41	38	39	39
SD	4	4	5	6	3	2	3	5	3.43	5.31	1.51	4.63	6	6	5	8	4	6
P	NS	NS	NS	NS	NS	NS	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	NS	NS	NS	NS	NS	NS

Note: Oxyg = Oxygenator; P_{O₂} = mean P_{O₂} mmHg; P_{CO₂} = mean P_{CO₂} mmHg.

TABLE 9. Pump Flow Rates, Radial Artery Pressures and Urine Output During Cardiovascular Pulmonary Bypass

Group	I		II		III	
	BO	MO	BO	MO	BO	MO
Oxygenator Flow Rates (ml/min)	3571	5295	3400	5300	3462	4616
SD	467	675	503	589	506	863
P	<0.002		<0.001		<0.01	
MRAP (mmHg)*	76	86	77	89	80	90
SD	11	11	12	11	10.2	3.77
P	<0.01		<0.01		<0.02	
Urine output (total ml)	494	562	873	843	851	1187
SD	201	235	454	439	495	633
P	NS		NS		NS	

*MRAP = mean radial artery pressure

ferences found in the urine outputs either during cardiopulmonary bypass or within the first 24 hours after operation.

Fluid and Blood Balance

After heparin was reversed by protamine sulfate, diffuse bleeding or oozing occurred in 16 patients who were operated upon with the BO and 8 patients with the MO. This resulted in an overall incidence of oozing in 35.5% of the BO and 17.3% of the MO cases. The postoperative blood loss during the first 24 hours is presented in Table 10. In Groups I and II the blood loss was significantly less with the MO than in the corresponding groups using the BO. Although no significant difference in blood loss between MO and BO was seen in Group III, it should be noted that BO in this group was heavily weighted toward coronary artery bypass procedures, while MO was heavily weighted toward prosthetic valve replacement, which usually results in more blood loss than does coronary artery bypass. Three patients required exploration for persistent postoperative bleeding. Of these, two were from Group II, one MO and one BO while the third patient was from Group III (MO). The patient from Group II MO had surgical bleeding after correction of a tetralogy of Fallot while the other two had only diffuse non-surgical oozing. There were no statistically significant differences in the volume of blood or crystalloids administered to these groups during cardiopulmonary bypass or postoperatively.

Hospital Complications and Mortality

All patients survived the operation itself. Of the 45

TABLE 10. Blood Loss During the First 24 Postop Hours

Group	I		II		III	
	BO	MO	BO	MO	BO	MO
Oxygenator Blood loss*	10.85	6.46	11.69	6.21	8.34	13.62
SD	7.9	4.8	6.5	6.79	6.31	8.52
P	<0.01		<0.01		NS	

*Mean blood loss (ml/kg/hr)

patients in Group I there were two significant early post-operative complications due to atelectasis (one MO and one BO). Of the 31 patients in Group II there were 5 complications (three BO and two MO). One patient (BO) had a myocardial infarction with low cardiac output two hours after operation and required intraaortic balloon counterpulsation. He expired on the second postoperative day. Another patient (BO) had transient left hemiparesis. The remaining three complications were due to mild temporary confusion (two MO and one BO). Of the 15 patients in Group III one patient (MO) had acute renal failure requiring hemodialysis with complete recovery. There was one death (BO) on the eleventh postoperative day secondary to hypotension and anoxic brain damage.

Comments

There have been numerous studies demonstrating the superiority of the MO over BO when used for prolonged cardiopulmonary support.^{3-5,11,14,18} However, there is little information available evaluating the membrane oxygenator for short-term cardiopulmonary bypass. This study compared the Travenol 5M0316 Modulung-Teflo[®] oxygenator with the Travenol 5M0314 Variflo[®] to determine whether the use of the MO for routine cardiopulmonary bypass provided the same benefits as demonstrated during prolonged support.

The results revealed that patients operated upon with MO had statistically significant higher flow rates, higher perfusion pressures, and more physiologic P_{O_2} and P_{CO_2} values during bypass. This relates, at least in part, to the capability of the MO to control oxygenation and carbon dioxide elimination separately which cannot be done with the BO.² The postoperative blood loss was also significantly less when the MO was employed. This appears to be due to better maintenance of platelet function by the MO as compared to the BO.¹⁷ The other measured parameters, such as plasma and serum hemoglobin levels, prothrombin activity, urine output, renal function and clinical course further emphasized the stability of the MO. Still another advantage in using the MO for "routine" cardiopulmonary bypass procedures is the occasional unpredictable requirement for prolonged circulatory support, for which the MO is far better suited than is the BO. The availability of this disposable oxygenator at a competitive cost and the satisfying re-

sults of this study prompted us to employ this membrane oxygenator for routine cardiopulmonary bypass.

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DISCUSSION

DR. KARL EUGENE KARLSON (Providence, Rhode Island): Our interest in this oxygenator began with our collaboration with Dr. Galletti and his group in laboratory testing, and we have used it clinically for about 15 months. It is also our preferred oxygenator. The microporous membrane has certainly increased the efficiency of the oxygenator. Changing from a silicone rubber membrane to the porous membrane increased

the oxygen transfer $2\frac{1}{2}$ times, and the CO_2 transfer by an even larger increment in this particular configuration of oxygenator.

Since I have heard that some groups have been disappointed with the performance of this oxygenator, it may be appropriate to comment on some of its idiosyncrasies. Our experience has taught us that attention to details of operation of this unit, as with all oxygenators, is essential.

The shim bag, which changes the internal pressure relationships of the oxygenator, is important to the performance. The shim pressure is, as Dr. Beall indicated, adjustable. Increasing the pressure makes the blood film thinner, but also changes the ventilation-perfusion relationships of the oxygenator and causes an internal gas shunt. Oxygen and carbon dioxide transfer are therefore influenced by the shim pressure, but carbon dioxide transfer is influenced to a greater extent by the rate of flow of oxygen through the unit.

We have demonstrated that carbon dioxide transfer may decrease with perfusion time, because water accumulates in the gas phase. This deterioration of carbon dioxide transfer is reduced by shortening the time during which a nonblood prime remains in the oxygenator before perfusion begins, and by ventilating the oxygenator with warm, dry gas.

With the shim pressure equal to input blood pressure, carbon dioxide transfer is optimal. Therefore, by waiting to prime the oxygenator just before bypass starts, ventilating with warm, dry gas, and adjusting the shim pressure to equal input blood pressure, we have found no decay of carbon dioxide transfer up to seven hours of clinical perfusion.

These factors, together with a large excess of carbon dioxide transfer capacity inherent in the oxygenator have resulted in most of our clinical perfusions being done with a very low oxygen flow rate to prevent respiratory alkalosis. We have not seen oxygen transfer decay.

May I mention another word of caution? We have resterilized two of these oxygenators in our hospital gas sterilizer after they were removed from the sterile wrappers, set up for perfusion, but not primed. We found that these two units did not appear to perform as well as the others. We do not yet know the reason for this lesser performance, but I call it to your attention if you ever to use a resterilized unit.

Now we have begun testing a smaller version of this oxygenator with half the membrane area of the oxygenator reported today. It has half the priming volume, 200 ml, half the gas transfer capability of the larger unit, and appears to be a suitable oxygenator for smaller patients.

I'm certain that microporous membrane oxygenators will be modified as time goes on, but we have found that this unit makes use of membrane oxygenators a routine, practical thing in our hospital.

DR. WATTS R. WEBB (Syracuse, New York): I agree that there are many virtues of the membrane oxygenator, but I just can't let a paper go by like this that lauds an instrument for the way in which it's being used, or being misused. I think many of the virtues that we have heard described are just because of a difference in use, and not a difference in the oxygenator.

When we talk about difference in flow rates, this is just the way the machine is being used, and is nothing intrinsic to the bubble oxygenator

or the membrane oxygenator. In the first place, coronary patients have a much lower blood volume than valve patients, and if, as we have been told, there is a difference in composition in the two groups, one is going to flow more than the other just by the intrinsic blood volume they have.

In addition, the degree of gravity is quite different, when one talks about the bubble oxygenator of the bag type they are using, and the membrane oxygenator they are using. This has nothing to do with anything except with the way they are used. Likewise, perfusion pressures naturally reflect the flow rate.

Similarly, the PO_2 can be regulated by either oxygenator to any level you want to put them, and this has nothing to do with the intrinsic of the oxygenator.

DR. JOHN E. LIDDICOAT (Closing discussion): In response to Dr. Karlson, we appreciate his comments and also thank him, and Dr. Galletti for their pioneering efforts in the development of this oxygenator along with their numerous other oxygenator contributions. In response to Dr. Karlson's statements, it is a little more difficult to set up the membrane oxygenator but once the pump team is attuned to the various parameters (arterial and venous reservoir, slave pumping, et cetera) this has not been a problem. It has worked out very satisfactorily.

We would like to reemphasize again the need for the use of heated, dry oxygen, thereby removing the water vapor before condensation can take place. If this is not done, the membrane can go into frank pulmonary edema.

In response to Dr. Webb's comments, we definitely didn't mean to imply that we were dissatisfied in any way with the bubble oxygenator. In fact, we have only been able to convert two of our rooms to the membrane and are still continuing to use the bubble oxygenator for many more cases than we are the membrane. However, we are continuing to strive for a more physiologic oxygenator.

In response to the differences in the group, we were hopeful—and maybe it was not apparent on the slides—that these groups were statistically significant. By the fact that the procedures were all done in the same operating room with the same team; we tried to eliminate the variable of different surgeons. After we had completed 50 cases with the membrane oxygenator, we thought it would be interesting to go back and retrospectively review the previous consecutive 50 cases using the bubble oxygenator in the same room. Therefore, we were hopeful of not skewing our statistics.

The gravity flow into the membrane and the gravity flow into the bubble oxygenator were the same.

The Surgical Treatment of Unstable Angina Pectoris

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Since the advent of saphenous vein bypass grafting as successful means of myocardial revascularization, a variety of coronary artery disease syndromes have come under surgical attack. The proper role of surgery in many of these coronary syndromes remains ill-defined. However, clear indications for surgical revascularization exist in patients with unstable angina pectoris, i.e., progressive angina and onset of rest pain and nocturnal angina in spite of adequate medical therapy. An analysis has been made of 100 consecutive patients with unstable angina pectoris who underwent myocardial revascularization over the past 2 years at the Woodruff Medical Center of Emory University. Included in this group are the following subgroups: 1) Emergency cases with preinfarction angina (including Prinzmetal angina); 2) Cases of combined valvular heart disease and coronary artery disease; and 3) Advanced coronary artery disease with certain complications of previous myocardial infarction. A discussion of the relative merits of saphenous vein grafts and internal mammary artery anastomoses is presented and indicates that the technique selected should be determined by the quality of the distal native coronary circulation. Surgical mortality and morbidity figures, patency rates of saphenous vein grafts and internal mammary artery anastomoses visualized postoperatively, and the number of patients with dramatic relief of angina pectoris in this series support current enthusiasm for available surgical techniques for myocardial revascularization.

SINCE the advent of saphenous vein bypass grafting as a successful means of myocardial revascularization a spectrum of coronary artery disease syndromes have come under surgical attack.^{1,5,10} The proper role of surgery in many of these coronary syndromes remains ill defined.^{6,8} However, strong indications for surgical revascularization exist in patients with unstable angina pectoris.^{3,10}

Unstable angina pectoris has been difficult to define in precise terms yet it is imperative that such a definition be made if the diagnostic and therapeutic efforts of different centers are to be properly compared and correlated.

In this report unstable angina pectoris has been defined by using a list of clinical subsets. The six subsets selected

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were: 1) initial onset angina (within 30 days) plus rest pain; 2) changing anginal pattern (pain with less exertion) without rest pain; 3) rest pain plus mild exertional angina; 4) rest pain plus disabling exertional angina; 5) prolonged pain (more than 30 minutes) without evidence of acute myocardial infarction in patients who have previously experienced brief pain; and 6) prolonged pain without acute myocardial infarction but with prior objective evidence of atherosclerotic heart disease. (Table 1).

One hundred consecutive surgical patients whose clinical profiles were defined by these subsets were analyzed using a computer assisted data pool consisting of all patients undergoing coronary angiography at Emory University Hospital.

Clinical Material

In a 14-month period from July, 1973 to October, 1974, 100 consecutive patients with unstable angina pectoris as previously defined underwent myocardial revascularization at Emory University Hospital. There were 81 men and 19 women in this group. Age range was 33 to 73 years (mean 54.2 years).

Sixty of these 100 patients had electrocardiographic evidence (significant 'Q' waves) of previous myocardial infarction. Coronary arteriography revealed significant (75% occlusion) single vessel disease in 23 patients, double vessel disease in 32 patients, triple vessel disease in 43 and left main disease in 10 patients. Eight of the patients with left main disease had other vessel involvement.

Preoperative ejection fractions could be accurately calculated in 86 patients. These ejection fractions were near normal in approximately one half of the patients but were significantly decreased in others (Table 2).

Left ventricular endiastolic pressure (LVEDP) at rest and two minutes post-angiogram are listed in Table 3. The

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1975, Boca Raton, Florida.

TABLE 1. *Definition of Unstable Angina Pectoris*

	Number
Initial onset angina + rest pain	6
Changing anginal pattern (less exertion) without rest pain	9
Rest pain + mild exertional angina	14
Rest pain + disabling exertional angina	53
Prolonged pain (more than 30 min) without evidence of AMI in patients who have had brief pain	8
Prolonged pain (more than 30 min) without AMI but with prior objective evidence ASHD	10
Total	100

normal LVEDP in 71 patients at rest and 45 patients post-angio demonstrated that severe left ventricular dysfunction was not a typical finding in these patients presenting with unstable angina pectoris.

Methods and Results

Myocardial revascularization was classified as emergency, urgent, or elective. Eleven patients underwent emergency coronary bypass immediately following coronary arteriography. These were patients experiencing prolonged pain (more than 30 minutes) without evidence of myocardial infarction (Printzmetal angina). Twenty-two patients were classified as urgent. Included in this group were patients with left main obstruction and severe effort angina plus rest pain. Sixty-seven patients were added to the elective operative schedule following cardiac catheterization and completion of preoperative evaluation.

Surgical Technique. A median sternotomy incision was employed in all cases. Mid and distal saphenous veins were harvested through multiple small incisions in the lower extremities. Cardiopulmonary bypass and moderate systemic hypothermia (28-32 C) were employed using a disposable bubble oxygenator. In some patients saphenoaortic anastomoses were performed using partial occlusion clamps applied prior to the institution of cardiopulmonary bypass and in others these anastomoses

TABLE 2. *Preoperative Ejection Fractions*

	Patients
↑ .6	41
.5-.6	18
.4-.5	17
.3-.4	8
.2-.3	2
not calculated	14
Total	100

TABLE 3. *Left Ventricular End Diastolic Pressure (LVEDP)*

	At rest	Post-injection
↓ 12	71	45
12 - 20	21	35
↑ 20	7	19
not calculated	1	1
Total	100	100

were performed during the phase of rewarming. Electrical fibrillation, induced if not occurring spontaneously, was used to facilitate the minimum dissection necessary for coronary artery exposure. The LV was sump drained in all cases. During the sapheno-coronary anastomoses the aorta was cross clamped for period of 20 minutes or less. At least 5 minutes of coronary flow was permitted between distal anastomoses when multiple bypasses were performed. Sapheno-aortic anastomoses were performed under normal vision or magnification (3.5 power) with 5-0 prolene in a running suture technique. Segments of saphenous vein were beveled to the desired degree and the resulting flaps were not trimmed but were employed to give a cobra head takeoff. A small button of aortic wall was removed at some but not all of the anastomotic sites. The sapheno-coronary and internal mammary artery—coronary artery anastomoses were performed with multiple interrupted sutures of 6-0 or 7-0 prolene placed under magnification (3.5 power).

Technique for Takedown of the Internal Mammary Artery. After the median sternotomy incision was completed, a small retractor was placed at the lower portion of the sternum and the left sternal border elevated as the retractor was opened. This maneuver elevated the entire left sternum without undue strain on the first assistant while the IMA was taken down. External counter pressure on the anterior chest wall invaginated the perforating branches of the internal mammary artery for better visibility. The internal mammary artery was dissected out with scissors and ligated at its distal portion (level of the sixth intercostal space). A pedicle of vein and artery approximately three-quarters of an inch in width was taken down entirely with the electrocautery. The internal mammary artery was dissected proximally to the level of the first rib. Once the pedicle had been brought down, inspection of the artery for proper diameter was made. Mammary arteries of less than 2 mm in diameter was deemed unacceptable for use. Three to four cc's of papaverine diluted one to six in normal saline was injected into the distal end of the mammary artery with a 21 angiocath needle. The suture was tied down, the angiocath removed, and the distended internal mammary artery laid aside for later use. The left anterior descending coronary artery was then dissected. The IMA usually will not reach below the mid-portion of

TABLE 4. Number and Type of Bypass Grafts

Saphenous Veins	
Single	20
Double	43
Triple	10
Quadruple	1
Internal Mammary Artery	
Isolated IMA	8
IMA + Single Vein	14
IMA + Double Vein	4

the LAD. Once the aorta was cross clamped and the left anterior descending coronary opened, calipers were used to make the arteriotomy incision in the LAD 4 mm in length. An oblique cut in the internal mammary artery was made 4.5 to 5 mm in length. A single 7-0 prolene suture is then used to construct the anastomosis and just prior to tying this suture, the bulldog clamp was removed from the IMA and the aortic cross clamp released. This distended the anastomotic site as the suture was then tied.

Flow rates were recorded using an electromagnetic flow meter. Artificial ventilation was maintained for a period of 12 to 24 hours. Anticoagulants were not employed on a routine basis. However, anticoagulation therapy was begun immediately if evidence of phlebitis was observed in the lower extremities.

The number and type of bypass grafts employed in this series are listed in Table 4. Twenty-eight patients received either a single vein graft or an isolated IMA graft. Thus, in 23 patients with single vessel disease complete revascularization was accomplished but only a single bypass was possible in 5 patients with double or triple vessel disease. Fifty-seven patients received double bypass grafts (32 patients with double vessel disease and 25 patients with triple vessel disease), triple bypass was achieved in 15 or 43 patients having triple disease. Our policy is to perform complete revascularization whenever possible, especially in critically ill patients. However this was not always possible in some patients with severe triple vessel disease due to total obstruction and obliteration or inadequate distal vessels.

A significant element of surgical morbidity was operative myocardial infarction. These infarctions were diagnosed by the appearance of new 'Q' waves in the postoperative electrocardiogram. This complication occurred in 16% of the patients. There was no apparent relationship between such infarctions and hospital course or survival. Six patients experiencing operative infarctions have been re-catheterized and demonstrated areas of decreased contractility in the postoperative ventriculogram not present in earlier studies. The instance of peri-operative myocardial infarction has been reported to range from 5 to 20%.^{4,9} The true clinical significance of these infarctions is unclear

but they must be accepted as a definite complication of revascularization surgery.

Surgical Mortality. Five patients (5%) died during hospitalization (Table 5). In two patients cardiopulmonary bypass could not be discontinued and these patients ultimately expired in the operating room. One patient died on the second postoperative day of complications of low cardiac output. Another patient expired on the eighth postoperative day from an acute aortic dissection apparently arising at the site of application of a partial occlusion clamp to the ascending aorta. The final patient expired on the tenth postoperative day of acute renal failure and other complications. All 5 patients had severe triple vessel disease. Four exhibited generalized ventricular hypokinesia and decreased ejection fractions. Two patients had a history of documented congestive heart failure. Two patients had experienced multiple myocardial infarction in their past. Two of the patients had triple bypass grafts; three patients had double bypass grafts.

Followup Studies. Fifty-nine of the 100 patients have returned for repeat coronary arteriography and ventriculography. Seventeen patients were studied one month postoperatively, as part of a study to establish our early patency rate. Failures (graft occlusions) during this interval are related primarily to technical failures and improper vessel selection. All asymptomatic patients were encouraged to return for later followup studies between one month and one year; to date 42 patients have had these later follow up studies. All patients who developed recurrence of symptoms were restudied. Therefore, the followup group presently includes routine early studies, surgical failures, and a group of co-operative volunteers for later studies.

Subjective Data. The effectiveness of bypass surgery in the relief of angina pectoris has been clearly demonstrated.^{2,5} Relief of angina pectoris in our patients compares favorably with reported experience. Seventy-three per cent of patients received complete relief of angina and an additional 19% were significantly improved. In 5% of the patients symptoms were unchanged and in 3% symptoms

TABLE 5. Surgical Mortality and Morbidity

Patients	100
Deaths	5 (%)
Operative 2 (%)	
Hospital 3 (%)	
Operative Infarctions	16 (%)
Mortality	
Patient, Day	Cause
H.P., 10	Acute renal failure
H.S., 8	Aortic dissection
H.W., 2	Low output syndrome
J.N., 0	Unable to come off bypass
M.T., 0	Unable to come off bypass

TABLE 6. *Graft Patency*

Number of Grafts	105
Total grafts patent	84 (80%)
One graft patent	24
Two grafts patent	24 (88%)
Three grafts patent	4
0 grafts patent	7 (12%)

were worse. In summary, 54 of 59 patients restudied up to a year following surgery were subjectively improved (92%).

Objective Data. The overall graft patency (Table 6) was 80% or 84 patent grafts out of 105 total grafts performed. Fifty-two patients (88%) had one or more functioning grafts at followup and 7 (12%) had no grafts patent.

IMA grafts have demonstrated a high patency rate.⁷ Twenty of our IMA grafts have been studied and 19 or 95% were patent. The single occlusion (5%) occurred in a woman with a mammary artery of questionable adequacy. It has been our policy to employ internal mammary artery grafts primarily for obstructive disease of the anterior descending coronary artery. If the distal LAD is of small caliber and the runoff poor, it is most desirable to use an IMA graft. If the distal vessel and vascular bed are of good size and quality, saphenous vein bypass may be selected, accepting the slightly lower patency rate in this anatomical situation in order to achieve the maximum increase in coronary blood flow. There is no doubt that flow rates with saphenous vein grafts are superior to flow rates with IMA grafts. Occasionally patients with patent IMA grafts continue to experience angina; angina with patent vein grafts is most unusual. Postoperative ejection fractions (Table 7) were quite similar to the preoperative studies. If 26 patients having ejection fractions greater than .6 before and after surgery are excluded, an analysis of 33 abnormal postoperative ejection fractions showed that 9 were unchanged, 6 were improved, 11 were worse and 7 were not calculated. The left ventricular endiastolic pressure was determined postoperatively in the resting and post injection states (Table 8). In the resting states, there were 42 normal values and 17 abnormal values. Of the 17 abnormal LVEDP's, one was unchanged, 6 were improved, and 10

TABLE 8. *Preoperative Ejection LVDEP*

Resting		Post-injection	
Normal ($\downarrow$ 12 mm)	42	Normal	19
Abnormal	17	Abnormal	40
Unchanged	1	Unchanged	5
Improved	6	Improved	20
Worse	10	Worse	15

were worse compared to preoperative values. In the post injection state, only 19 LVEDP's were below 12 mm Hg and 40 were abnormal compared to preoperative post injection values. Five were unchanged, 20 were improved and 15 were worse. This data suggests that a ventricle under stress may demonstrate evidence of improvement secondary to revascularization which is not apparent in resting studies.

Discussion

In an attempt to clarify the definition of unstable angina pectoris, clinical subsets were defined prior to study. Patients so classified ranged from those with moderate exertional pain and episodes of rest or decubitus pain to prolonged episodes of pain with transient EKG changes which did not progress to extensive myocardial infarction. Identification of and separation into clinical and anatomical subsets should allow a clearer delineation of those patients who will benefit most from myocardial revascularization.

Single vessel disease is unusual in patients with unstable angina and even more unusual when rest pain is present. Therefore adequate revascularization for unstable angina usually involves double and triple bypass grafts.

There are advantages and disadvantages to both saphenous vein and IMA grafts. The IMA grafts offer the higher patency rate (95% vs overall rate of 80%). The IMA grafts are limited in this experience to the management of proximal lesions of the LAD. Flow rates achieved with IMA grafts are generally lower than flow rates with saphenous vein grafts and may be inadequate for the total relief of angina in patients with a severely ischemic left ventricle. Saphenous veins offer the advantages of multiple grafts to distal sites of all major coronary arteries. In general, saphenous vein grafts are indicated for lesions of the distal right and circumflex coronary arteries and for LAD lesions if the distal vessel and vascular bed will permit the high flow rate necessary for vein graft patency. IMA grafts are preferable only for proximal LAD and diagonal lesions with small distal vessels and poor runoff. Saphenous vein grafts properly employed demonstrate a patency rate which is only slightly inferior to IMA patency rates and provide maximum increase in coronary blood flow.

TABLE 7. *Postoperative Ejection Fractions*

Normal ($>$.6)	26
Abnormal	33
Unchanged	9
Improved	6
Worse	11
Not calculated	7
Total	59

Myocardial revascularization is effective in the relief of angina pectoris (73% of patients with complete and 19% with partial relief of angina). This dramatic relief of pain permits a return to normal activities in over ¾ of patients favoring coronary bypass surgery. Relief of pain correlates well with graft patency rates.

Surgical results show little impact of myocardial revascularization over ventricular function except in those cases where acute ischemia was present at the time of the preoperative ventriculogram (improved) or when operative infarction occurred (worse). Data suggest that stress testing may demonstrate an improvement in ventricular function secondary to myocardial revascularization not apparent in the resting state. Undoubtedly, the greatest impact of myocardial revascularization on patient survival will be demonstrated on those patients with double, triple, and left main disease.

Conclusions

Unstable angina pectoris must be separated into clinical subsets to permit future definition of patients who will benefit from myocardial revascularization.

Patients with unstable angina pectoris, even in emergency circumstances, undergo myocardial revascularization at acceptable low operative risk (5%).

DISCUSSION

DR. WALTER JANKE (Fort Lauderdale, Florida): (Slide) Our total experience, prior to coming down to Florida, encompasses 543 consecutive patients, with a mortality of six patients, or 1.1%. On 27 of these patients, preinfarction was a prime indication for surgery. Six of these patients went ahead and developed acute infarction a few hours before or during induction of the anesthetic. Two of those patients required external and internal cardiac massage during cannulation. An additional patient had an acute infarction, went into cardiac shock, had to have a cardiac catheterization while in cardiogenic shock. Subsequently, we took him to surgery within three hours, and he survived the procedure.

As we see, 16 patients had valvular replacement. We lost two of those patients.

(Slide) Of the patients with valve replacement, three had mitral valvular replacement, 11 had an aortic valvular replacement, and one was a triple bypass. One patient had an open mitral commissurotomy.

(Slide) We feel that probably the most important factor in the selection of patients for coronary artery surgery is the run-off, distal to the area of obstruction. We don't consider that congestive heart failure or elevated end diastolic pressure are a contraindication for surgery, if they do have a good run-off distal to the area of obstruction. I would like to know Dr. Hatcher's opinion in this respect.

DR. CARLOS M. CHAVEZ (Jackson, Mississippi): I think we are now in need of a redefinition of what is called "unstable angina", and to limit the term of unstable angina to those cases where there is solid evidence of a pre-infarction state.

In our experience, we have been unable to document a case of unstable angina with single vessel disease except for left main artery disease. Most of our cases have been of double, triple, vessel involvement, in the presence of dyskinesia, severe arrhythmias, and so forth.

I was a little surprised that Dr. Hatcher's series did not include any case

Myocardial revascularization is quite effective in relieving anginal pain, but has little demonstrable effect on ventricular function in resting states.

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of ventricular aneurysms, which are very commonly associated with multiple vessel involvement, which is also the case for patients with unstable angina. I would like to ask him whether he has in his series, any of these cases which required the management of ventricular aneurysm as well as the bypass grafts.

DR. GEORGE C. MORRIS, JR. (Houston, Texas): My comments are related primarily to patency rates. My own series exceeds 2000 in the last seven years, and in analyzing followup arteriograms in over 200 patients, most of whom had problems, the patency rate is 93%, excluding small secondary branches, such as the diagonal and distal branches of the right. I believe we should all be able to achieve a patency rate of this category with the saphenous vein; and this is comparable to the experience with the internal mammary. In the case of the internal mammary, one is usually working with the ideal recipient artery, the left anterior descending, which, as we all know, has the highest flow rates.

DR. H. NEWLAND OLDHAM, JR. (Durham, North Carolina): We have been interested in the meaning of perioperative myocardial infarction. I noticed an incidence of 11% in this series of patients. We consistently have found that approximately 20% of our patients have EKG evidence of myocardial infarction, and a significantly larger number have CPK-MB isoenzymes present during the perioperative period, indicating degrees of myocardial damage.

We have evaluated recently 65 of these patients, one year following their surgery, with complete cardiac catheterization, selective angiography, and evaluation of ventricular function. We specifically were interested in those patients with EKG changes and those with CPK-MB evidence of myocardial damage at the time of operation.

We were unable to demonstrate any statistical differences in functional classification, the results of treadmill exercise testing, graft patency rates or changes in ventricular function between patients with or without evidence of perioperative myocardial damage.

I wonder if this has been your experience, and am interested in the postoperative course of your patients with myocardial infarctions.

DR. CHARLES R. HATCHER, JR. (Closing discussion): Dr. Janke, your results are, of course, excellent. We have your feeling that the patency rate of either vein or internal mammary artery is in large part related to the quality of the vessel and the distal vascular bed.

This overlaps a bit with my reply to Dr. Morris' comment, that a patency rate of over 95% can be achieved with saphenous veins.

Even if we limit our comparisons to veins to the left anterior descending coronary artery, I have still been unable to achieve a 95% patency rate.

So we feel that there is a small inherent patency advantage with the internal mammary. The basic philosophy that Dr. Jones has employed—and it is he who has done these internal mammary anastomoses—is as follows. If the vessel is small in diameter, and the vascular bed distally quite poor, we feel that the internal mammary artery is the vessel of choice. On the other hand, if the LAD is of adequate size and the run-off rather good, we would prefer a saphenous vein because of the increased flow that can be achieved with the saphenous vein, compared to the internal mammary artery.

We individualize these cases, and I can only congratulate George on a 95% patency rate with his saphenous veins, and that gives us all a target

to shoot for. We can achieve this with internal mammary arteries, and perhaps with saphenous veins, if we have the selection that I have mentioned.

Dr. Chavez, it was my original intent to have 100 consecutive patients called from our computer pool who had presented with unstable angina, but Dr. King, one of the co-authors, who is a cardiologist, pleaded that we should keep the group as homogeneous as possible. For that reason we excluded patients with ventricular aneurysm and valve replacement.

There was 12 such patients. Ten had aortic valve replacement as well as one or two saphenous vein bypasses. All of those patients survived, and have done very well. But in making a maximum attempt here to try to define unstable angina, we omitted those.

Newland, the 11% was in the 59 patients who returned for detailed studies. In our overall experience, the operative infarction rate has run around 16–18%, a figure more closely identified with your values. As far as we can determine, there has been no effect on hospital course and behavior of these patients who have demonstrated these operative infarctions. But as you have mentioned, when some of these patients are brought back for study, we find that the ventriculogram and ejection fraction are not as good as they were previously.

So we feel that, although they may not have the significance of myocardial infarction occurring in other settings, it is also true that they cannot be entirely ignored. And I'm afraid that they occur a little more frequently than most surgeons have cared to admit.

Quality, Quantity and Distribution of Medical Education and Care:

Regulation by the Private Sector or Mandate by Government?

W. G. ANLYAN, M.D.*

The public, the federal government and most state governments have become increasingly concerned with the lack of access to primary care as well as the specialty and geographic maldistribution problems. Currently, there is a race in progress between the private sector and the federal government to devise solutions to these problems. In the federal sector, varying pieces of legislation are under active consideration to mandate the correction of specialty and geographic maldistribution; proposals include: 1) setting up federal machinery to regulate the numbers and types of residencies; 2) make obligatory the creation of Departments of Family Practice in each medical school; 3) withdraw current education support from medical schools causing tuition levels to increase substantially—federal student loans would then provide the necessary leverage to obligate the borrower to two years of service in an under-served area in exchange for loan forgiveness. In the private sector, for the first time in the history of the United States, the five major organizations involved in medical care have organized to form the Coordinating Council on Medical Education (CCME) and the Liaison Committee on Graduate Medical Education (LCGME). One of the initial major endeavors of the CCME has been to address itself to the problem of specialty maldistribution. The LCGME has been tooling up to become the accrediting group for residency training thus providing an overview of the quality and quantity of specialty training. It will be the intent of this presentation to bring the membership of the Southern Surgical Association an up-to-date report on these parallel efforts. The author's personal hope is that the private sector can move sufficiently rapidly to set up its own regulatory mechanisms and avert another federally controlled bureaucracy that will forever change the character of the medical profession in the United States.

THE MEDICAL MANPOWER problems of concern to the Public, to the Congress and to most State Legislatures include the following: 1). The adequacy of the

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number of physicians; 2.) The question of excessive importation of foreign medical graduates, especially from medical schools that are not comparable in their standards to those in the United States; 3.) The specialty maldistribution problem and, in particular the lack of access to primary care physicians; 4.) The geographic maldistribution problem; 5.) The role and responsibilities of physician extenders and the lack of categorization of physician extenders; the overlapping roles of nurse practitioners and physician assistants; 6.) Quality control measures to be used throughout the continuum of medical education and practice.

The Adequacy of the Number of Physicians

Between 1961 and 1969, there appeared to be a unanimous opinion of the major associations interested in medical education as well as the federal government that there was a "shortage of physicians of crisis proportions." Under the stimulus of this "crisis" the number of medical schools was expanded to the present 114 in the United States. Class sizes were increased in most of the medical schools in the nation. The Physician Augmentation Program in 1969 further increased class enrollment by almost 1,000 entering students in less than a year. Despite this "crisis" in the 1960's, in 1973 the Department of HEW began to raise questions as to whether we "already had enough physicians in the pipeline" with the increases in enrollment that had been effected. As yet in 1974, a clear-cut policy statement has not come from the private sector regarding the adequacy of the number of U.S. physicians either in practice or "in the pipeline." Such a position cannot be taken without considering the numbers of foreign medical graduates who are entering

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the United States each year; many U.S. leaders have expressed grave concern at the revelation that, in 1973, 49% of physicians licensed in the United States were foreign medical graduates. Obviously, as controls are placed on foreign medical graduates entering the United States in future years, it would be anticipated that the number of U.S. graduates would have to be increased proportionately. Furthermore, the number of physicians needed is also dependent on the numbers of physician extenders introduced into the system. The use of different types of extenders and their relative responsibilities have yet to be defined in the civilian sector of the United States. It is the personal opinion of the author that it would be reasonable to plan to increase the number of admissions to U.S. medical schools by 10% over the September 1974 figure in the 5 year period 1975-1979. Adjustments can be made in subsequent 5 year periods as changes occur in the practice of medicine, in national policies regarding foreign medical graduates, in the use of physician extenders, etc.

It should also be noted that the use of overall physician-population ratios is a very inaccurate reflection of the true state of available medical care since it does not reflect the geographic or specialty maldistribution problem.

Foreign Medical Graduates

Most people are in agreement currently that it is a grave source of embarrassment to this nation to be so highly dependent on foreign medical graduates. Foreign medical graduates fall into two categories: 1) those who are U.S. citizens who have studied abroad because they have been unable to secure a position in a U.S. medical school; and 2) foreign nationals graduating from foreign medical schools. Category 1 should be phased out as quickly as possible and the Cotrans Program should be looked upon as a temporary expediency to accommodate this group of U.S. nationals into the U.S. medical system; it should also be noted that most students falling in this category are not the layer of students who just "missed out" being admitted to U.S. medical schools. It is a layer of students well below that level who have the economic means to go and study abroad. Concerning category 2, with regard to foreign nationals who are FMGs, there should be a marked reduction in the numbers being admitted to the United States by controlling the number of residency slots available in any given year.

All foreign medical graduates should be subject to the same examination and licensure screening procedures that are used for graduates of U.S. medical schools. For foreign medical graduates, the highest priority should be given to those persons who are apt to return to their native countries to help improve the quality of medical education in their country.

In the Rogers legislation which is in the House,¹ the

current proposal of limiting the number of residencies to 125% of U.S. graduates in any given year would allow for any lateral mobility of U.S. graduates who wished to shift from one field to another and would also provide for a small number of foreign medical graduates to enter our residency training programs.

Specialty Maldistribution

There seems to be a fairly broad consensus that the number of primary care specialties should be expanded; these include general medicine, general pediatrics, and family practice. At the present time, these combined specialties command about 35% of the filled residency programs. It has been recommended by the Coordinating Council on Medical Education that this number be expanded to 50% of the graduates. It would also be necessary through the Residency Review Committees to eliminate programs on chronic probation. At the present time, it is interesting to note that there are many institutions that have several residency programs that have been on probation for a number of years. Such institutions should be examined carefully by the Liaison Committee on Graduate Medical Education regarding the adequacy of the institution to provide graduate medical education.

It is suggested that, under the aegis of the Liaison Committee on Graduate Medical Education and the Coordinating Council on Medical Education, residency positions be limited to 125% of U.S. graduates in any given year as proposed in the Rogers legislation¹ described above.

In working out a scheme to develop "reasonable quotas" for specialty training, all available data such as through SOSSUS (Study on Surgical Services for the United States) and AMA data on specialty manpower, should be used. Furthermore, the "reasonable quotas" should be geared to broad regional needs rather than purely on a national basis.

Geographic Maldistribution

The question has been raised recently by a non-physician educator as to who is maldistributed, the population or the physicians. Furthermore, he asked whether the person who by his free choice decides to live in a small locale on top of a remote mountain or a rural area should have the right to demand readily available medical care or, for that matter, the services of other comparable professionals such as lawyers, engineers, etc. In any event, this is a philosophic question, and in a pragmatic sense we have to look at the problems of geographic maldistribution with particular reference to rural areas and urban ghettos. It is suggested that we do the following to adjust the geographic maldistribution problem in a free society such as in the United States: 1). Optimize the use of non-physician manpower; 2). Intertwine the sys-

tem of health care and health education such as through the Area Health Education Centers to make rural areas more attractive for physicians and health care personnel; 3). Improve communications and transportation as was done so successfully by the military during the Korean and Viet Nam Wars; 4). As a last resort, use economic incentives and disincentives to entice people to settle in maldistributed areas.

Of debatable value in the current proposed legislation is the National Health Service Corps. When it was proposed in the late sixties, it was to provide for young men an alternative to serving in the military. However, today it would be looked upon as an obligation imposed only on a small segment of society; namely, physicians, dentists, and osteopaths. The question has been raised whether all young persons should not devote two years of their lives to the service of their country and not limit such service to those providing medical and/or dental care.

Physician Extenders

We need to define "who should do what to whom, where and when in health care." There are a burgeoning number of health professionals and sub-professionals in the system. There is a lack of categorization of roles, responsibilities, degree of dependence or independence of health practice. It is proposed that we categorize health personnel by their educational level and with regard to relative dependence of practice versus independence. Such categorization might be in five layers: 1) the pre-collegiate sub-professional; 2) a bachelor of health sciences for RNs, physician assistants, technologists, etc.; 3) a master of health sciences for nurse practitioners, advanced physician associates, physical therapists, health administrators; 4) a doctor of health science or M.D. for those with advanced degrees; and 5) the possibility of a final university-type degree at a doctoral level at the completion of residency training.

Quality Control

As indicated above, all foreign medical graduates should go through the same quality control process in examinations and licensure as graduates of U.S. medical schools. It is noteworthy that at the present time there is a vigorous debate about the future role of the National Board of Medical Examiners and especially their recent Goals and Priorities Report. There are many who feel that the current layering of Parts I, II and III should continue. There are others who have raised the issue as to whether an examination at the conclusion of the undergraduate component of medical education is not sufficient to replace both Part I and Part II with a subsequent examination at the completion of residency training. There is also a debate between a national process of examination in the private sector versus state examinations. To complicate the issue further, Senator Ken-

nedy's proposed legislation² would establish a federal governmental mechanism for certification.

The Specialty Boards should be left intact since they have done an excellent job in changing with the times and fulfilling their responsibilities. The only major issue is whether doctors of osteopathy should be admitted to the graduate medical process or not. This latter subject is under active discussion by the various boards at the present time.

Re-certification should become mandatory at an appropriate date for all physicians. It should be based on physician performance in the perimeter of practice to which the individual physician has confined himself or herself and not a re-taking of the specialty Boards. It is hopeful that PSROs (Professional Standards Review Organizations) will be managed by medical personnel as an additional peer review mechanism ensuring quality control.

Who takes the Lead to Institute and Manage the Systems Suggested Above?

The question needs to be raised as to whether the private sector is going to fulfill the needs of society by self-regulation or whether it should abdicate its role to the federal government and the Department of HEW, in particular. After several years of negotiation, the five major medical and health associations formed the Coordinating Council on Medical Education. The five organizations were the American Medical Association, the Association of American Medical Colleges, the American Board of Medical Specialties, the American Hospital Association, and the Council of Medical Specialties Societies. In addition, there is one person on the Coordinating Council (Assistant Secretary for Health Affairs-HEW) representing the federal government, as well as one person representing the public. The objective of the parent organizations was to establish a voluntary system for coordination and direction of accreditation of all levels of medical education and selected areas of allied health education. More specifically, the Coordinating Council on Medical Education has the following functions: 1). To develop and review policy; 2). To implement policy after adoption by the parent organizations; 3). To review and coordinate liaison committees; 4). To recommend studies and improvements.

The Coordinating Council on Medical Education has reporting to it the Liaison Committee on Medical Education, which accredits pre-M.D. medical schools, and the Liaison Committee on Graduate Medical Education. It has been proposed and accepted that a Liaison Committee on Continuing Medical Education be formed; it is anticipated that such a Liaison Committee will be functioning by July 1, 1975.

What is the alternative to the Coordinating Council on Medical Education regarding the development of national

policy in the private sector? Is it possible that the Coordinating Council will not be able to function because of the entrenched "political" positions of each or most of the parent associations? Should that happen, the alternative for the private sector would be the formation of a Commission on Medical Education and/or Medical Care supported and sponsored by some of the major foundations interested in medicine and health. In essence, the private sector has a little over two years to move into a position of leadership not only with broadly accepted plans for correcting the societal needs but staged implementation thereof. As has been evident in recent legislation proposed by Senator Kennedy,¹ it is his feeling that the private sector will never be able to solve these prob-

lems. In essence, that is what occurred in Canada and these issues were mandated by the provincial governments outside of the private sector.

Once we abdicate our responsibilities to the federal government, it will never again be possible to come to grips with the management of these issues in the private sector. As we can note from other such solutions controlled by the federal government, they are very apt to come under political pressures for political solutions rather than what is best for the health care of the nation.

References

1. Health Manpower Act of 1974; H. R. 17084.
2. Health Professions Educational Assistance Act of 1974; S. 3585

DISCUSSION

DR. WILLIAM R. DRUCKER (Charlottesville, Virginia): Bill Anlyan has given an absolutely magnificent survey of a most difficult problem, and we could spend the rest of the day and only begin to touch the surface of the many subproblems that his talk raises. But there are two that I thought I'd mention as a followup of his remarks.

One should know that the leader has been, and is, Bill Anlyan. As Dave Sabiston mentioned, he was the first Chairman of the Coordinating Council, and his counsels are still being actively used in the AAMC and the Coordinating Council, but he needs help. He needs help in many areas, but let me just mention two.

One problem that he did not discuss—he only had ten minutes—but intertwined throughout the entire fabric of his talk is the issue of cost.

Now, there have been two excellent studies completed in the last two years on the cost of educating a medical student. To my knowledge, there has been no study of the cost of educating a resident. But all of these are costs society must bear, and society is becoming increasingly concerned about this component of the total health industry: the cost of educating the people who function in it. And many of the decisions that are going to be made are going to be made in terms of what's the least expensive cost to achieve a particular objective.

I think here's a point where the private sector had better get busy, and become very cognizant of what the costs are. And then, are we willing to assume these costs, or are there better ways to achieve the same goals in education at lesser cost?

As you will see in Bill's abstract, he has identified some of the little plums that are being put before us now where the cost of medical education can be picked up by the federal government in return for certain commitments from the medical schools. Are we willing to accept these commitments?

These are issues that are at the very forefront of all medical schools today, and must be debated and must be solved. We have a chance to decide whether we are going to assume by other mechanisms some of these costs, or should they be picked up by the federal government? The issues are not clearcut, but they do involve costs.

Now, there is another issue that I think should be looked at; and that is, when Bill calls for help to solve the problems, he is not calling only for the people in medical schools. These problems are far too complex and far-reaching to involve just those of us who selected medical education as the thing we wanted to spend most of our time doing.

Medical education today is no longer just the problems of the medical school. It now belongs—and has belonged—in the community hospitals. It belongs in the sector of the practicing physician as well. So these issues are not those that can be looked at only by one or two people in the medical schools. They belong to all of us in the health profession.

The final point I would make—and I think this is a criticism of our health profession. When we are talking about where are we going, one of the additions I would have put on the first slide: We have not defined our goals. Our whole orientation has been allopathic medicine, to do the thing we love and know we can do well, and that's taking care of sick people. But we have paid much too little attention to prevention.

If we don't get after this, society and government planners are going to get after it. There is a huge area of work to be done in how to keep people from getting sick. The ABEX that Bill talked about is a step in that direction.

So as we talk about costs, as we talk about solving these problems involving the entire medical profession, let's re-examine our goals, and recognize that there is one we have neglected terribly. We have very little time to get after the problem, but let's get after it as the private sector, I would add. Let's look at our goals again and see that there's a much broader issue than just taking care of sick people—which is terribly important. Let's never downgrade that. Let's advance that. But also, let's look at the sector of keeping people from getting sick.

DR. FRANK C. SPENCER (New York, New York): First, I would like to express my appreciation to Dr. Anlyan for this report. In complex socioeconomic times like these, it is much more attractive to talk about a simple, precise problem, like alternate methods of treating fractures of the femur, rather than a vague, perplexing, ill-defined subject such as the quality of surgical care, foreign medical graduates and the like.

Also, I want to compliment the Program Committee as well for including this manuscript on the program, and suggesting, because such subjects are of such overwhelming importance, that the Program Committee seriously consider each year inclusion of one or more papers on these subjects. If someone with Dr. Anlyan's initiative does not submit an abstract, a status paper could be requested by the Program Committee regarding developments in a critical area.

Hence, for the next two to three years, at least, I would strongly endorse giving high priority on our annual program for such presentations.

DR. EDWARD S. STAFFORD (Lutherville, Maryland): I too would rise to congratulate Dr. Anlyan, who has done so well with this difficult subject, and to add one point. A great deal of attention must be paid not only to costs, as indicated by Bill Drucker, but also to the sources of the money.

As surgeons and as physicians, we have indeed, I think, been too parochial, in that we are now looking to what we do in our own activity. But we must enlist the support of all of the groups who are involved in paying for medical care; the huge insurance companies, the unions, local governments, and employers of large numbers of people, without whose support and backing we can neither do what we want, nor have a persuasive voice in the future.

If we try to do this on our own, but expect the federal government to supply the funds, we then are just in inescapable trouble.

PROFESSOR J. PHILIP SANDBLOM (Lausanne, Switzerland): It is with a feeling of frustration and deep emotion that I listened to this outlook for American medicine, because we have seen the same thing happen in Sweden, and one could hope that you will not have to go exactly the same road.

I think though that it will be difficult for you to avoid, because the modern society has a tremendous tendency to develop a powerful central

bureaucracy which all too often likes to throw the opinion of the medical profession in the wastebasket. This has led to some unhappy developments, both for doctors, patients, and for the society.

A small example. In an effort to diminish the staggering costs for medical care, the central bureaucracy has thought it a good idea to have more cases treated as outpatients. Their way of effecting this idea which is not without merit is brutal and drastic. Most of the young doctors with a surgical experience of 8-15 years are being expelled from the surgical departments and forced to join outpatient clinics. It is a tragedy for most of them and it also deprives the surgical departments of some of the most valuable collaborators.

There is also a tendency to exaggerate democracy. Our departments of academic surgery are now being run by a chairman who is not necessarily the surgeon of the department. It's rather run by a committee consisting one-third of teachers, one-third of employees—nurses and orderlies—and one-third of the students. They elect the chairman between them. If this is not always the best way of running it, it is in any case very time consuming.

I think it is absolutely necessary to keep some of the decisive power within the medical profession, in close collaboration with enlightened administrators. One has to foresee a development, and perhaps even accept some organization, which might somewhat limit the freedom of doctors and surgeons.

In exchange we should be allowed to participate in the necessary reforms for the best not only of our selves but also of our patients and of the society.

Doctor Anlyan's efforts should be an example to all of us.

DR. WORTHINGTON G. SCHENK (Buffalo, New York): I wonder if, in closing, Bill could give us some advice for when we go home. Clearly, in the next two years we are not going to be able to solve this long list of problems, but, hopefully, we might be able to solve some part of one of them, and in so doing, perhaps, influence the governmental agencies that we are able to accomplish something.

Bill, which of these are we most likely to solve? What is your advice to us?

DR. GARDNER W. SMITH (Baltimore, Maryland): I would like to point out that many of the suggestions for solutions which Dr. Anlyan has given us in these slides were incorporated in the questionnaire sent out by the AAMC just last week. I hope that those of us who can get our hands on that questionnaire will give the kind of support to the AAMC that will help us solve some of these problems.

DR. SAMUEL M. DAY, JR. (Jacksonville, Florida): As a delegate to the AMA, and we have a few others here who were delegates in Portland last week, I would like to commend Dr. Anlyan on his remarks. Also, I would like to urge that we try to keep our groups coordinated. At times our government seems to have attempted to divide the medical schools and the AMA. Liberal Public Health physicians as well as ultraconservative private practitioners have disagreed with AMA policy and organized their own groups which further divide organized medicine. This seems to

emphasize the universality of the AMA since both extremes are unhappy.

Last week in Portland the House of Delegates argued for eight hours over raising AMA membership dues. We finally settled for an assessment of six dollars which is hardly adequate to do what needs to be done. Maybe we are a bit shortsighted when we consider the fact that as one of the highest income groups we are paying less than nine dollars a month for our AMA dues. Airline pilots are said to pay \$60 a month. A linotype operator to whom I talked said he pays 1% of his gross income for local dues and 2½% for national dues (which include some extra benefits).

It is foolish, that in inflated times like these we should hesitate to raise our dues when the jobs that need to be done are so vitally important. When we return home I suggest we make every possible effort to maintain coordination between our groups. Support those who are fighting our battles and help assure adequate income for our AMA to do its job right; since we individual doctors are the AMA, let us take an active part in helping get AMA jobs done.

DR. WILLIAM G. ANLYAN (Closing discussion): Dr. Drucker is absolutely correct, in terms of the fact that the federal government is trying to put the maximum pounds per square inch today on the wrong end of the continuum of medical education; namely, on the poor entering medical student. He is also so correct on preventive care. Just in mental retardation alone we have \$80 billion problem in a half-way technology. We do need better institutions to take care of these youngsters; we need to continue the research to get down to the cause of mental retardation.

Dr. Spencer is correct on the follow-up needs of every one of the private associations to keep up with these on-going problems.

With regard to Ed Stafford's comment, the biggest leverage that the federal government may have on us is coming around the corner this next year. The new Chairman of the Ways and Means Committee has stated that one of his two foremost priorities is going to be a form of national health insurance; and we must make sure that it is an amalgam of private/public system, and not a public system alone.

Professor Sanblom is very correct in what he has told us. We must learn from the lessons of Scandinavia and the United Kingdom. As a matter of fact, many of the problems I have put on the board on slide No. 1 are yet unsolved in those particular countries, despite a nationalized, socialized system.

With regard to Dr. Schenk's and Gardner Smith's and Sam Day comments, it is terribly important to row together. Those five parent organizations are "us," and most of us, in one way or another, belong to them or have colleagues who are our representatives on them: the AMA, the Council of Medical Specialty Societies, of which most of you are members, like the American College of Surgeons, the Board, the hospital directors of our hospitals, who belong to the AHA, and the faculties of the schools of medicine, who belong to the various councils of the AAMC.

So the thing to do is to go home and not leave it up to that hospital director or to the dean or the vice president, but make sure that your voice is heard through your representation in your institution.

Surgical Management of Menetrier's Disease With Protein-losing Gastropathy

H. WILLIAM SCOTT, JR., M.D., HARRISON J. SHULL, M.D., DAVID H. LAW, IV, M.D.,
HENRY BURKO, M.D., DAVID L. PAGE, M.D.

Three patients with Menetrier's disease and protein-losing gastropathy who were studied during a 12 year period have been presented. The characteristic findings which differentiate them from patients with hypertrophic hypersecretory gastropathy, including the Zollinger-Ellison syndrome, are: 1) hypertrophy of gastric mucosa with giant rugal folds involving the fundus, cardia and body of the stomach but sparing the antrum; 2) mucosal hypertrophy consisting of gastric mucus-secreting cells while parietal cells and chief cells are diminished in number and may be absent from many microscopic sections; 3) gastric secretion of large volume containing excess mucus, low to absent hydrochloric acid and protein concentration 5 or 6 times normal (1.7 mg/ml); 4) hypoalbuminemia and hypoglobulinemia due to loss of serum proteins from gastric mucosa into the gastric lumen; 5) rare association with gastric ulcer. Unlike the Zollinger-Ellison syndrome none of our patients had duodenal ulcer or multiple endocrine adenomatosis or a family history of these conditions. We have found no authenticated reports in the literature which document a relationship of Menetrier's disease (as defined above) with multiple endocrine adenomatosis. Menetrier's disease with protein-losing gastropathy is a potentially lethal disorder of unknown cause with no specific treatment. Resection of the site of gastric protein losses as first done by Waugh¹ is logical and effective. One of our three patients died in hospital before gastrectomy was done. Two others have done well for 11 months and 12 years, respectively, after total gastrectomy with Roux-en-Y esophagojejunostomy and Hunt-Lawrence jejunal pouch.

THE ETIOLOGY of giant hypertrophy of the mucosal folds of the stomach, which is sometimes associated with severe protein losses and hypoproteinemia, is understood no better today than when described by Menetrier¹¹ in 1888. In Menetrier's lucid article he pointed out that adenomatous transformation of the gastric glands could present in two distinct forms: first, as circumscribed polyps of the stomach to which, when multiple, he applied the term *polyadénomes polypeux*; second, adenomatous transformation could present in the form of hypertrophied plaques of mucosa either limited or diffuse to which he applied the term *polyadénomes en nappe*.

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Today the eponymous term, Menetrier's disease, is usually applied to giant hypertrophy of the mucosal folds of the stomach which may or may not be associated with loss of protein from the mucosa.¹⁰ In Menetrier's disease the mucosal hypertrophy involves the fundus and body of the stomach and excludes the antrum. The gross appearance of the thickened gastric rugae resembles the convolutions of the brain. This disease must be distinguished from the mucosal hypertrophy of the Zollinger-Ellison syndrome and from the form of hypertrophic gastritis to which Schindler¹⁷ gave the name *hypertrophic glandular gastritis* and which Stempien²² classified as *hypertrophic hypersecretory gastritis*. In addition, gastric lymphoma and carcinoma must be excluded in differential diagnosis. On a clinical basis, the differential diagnosis of Menetrier's disease may be quite difficult. This remarkable disease is said to have an increased incidence in some families with multiple endocrine adenomatosis^{9,18,23} but unlike the Zollinger-Ellison syndrome it is uncommonly associated with peptic ulcer.^{3,12,15} The exudative gastric protein losses which may occur can cause life-threatening profound hypoproteinemia despite large increases in albumin synthesis and turnover rate.^{4,19}

During the last 12 years, three patients with this combination of Menetrier's hypertrophic gastropathy and severe protein-losing syndrome have been identified, studied and treated at Vanderbilt University Medical Center. Experience with these patients has prompted this report.

Case Reports

N.B., a 36-year-old Caucasian tile plant foreman, was admitted to the Vanderbilt University Hospital for the first time in January, 1962 complaining of generalized edema.

Present illness. Two weeks prior to admission the patient developed a cold with myalgia, weakness and non-productive cough and received

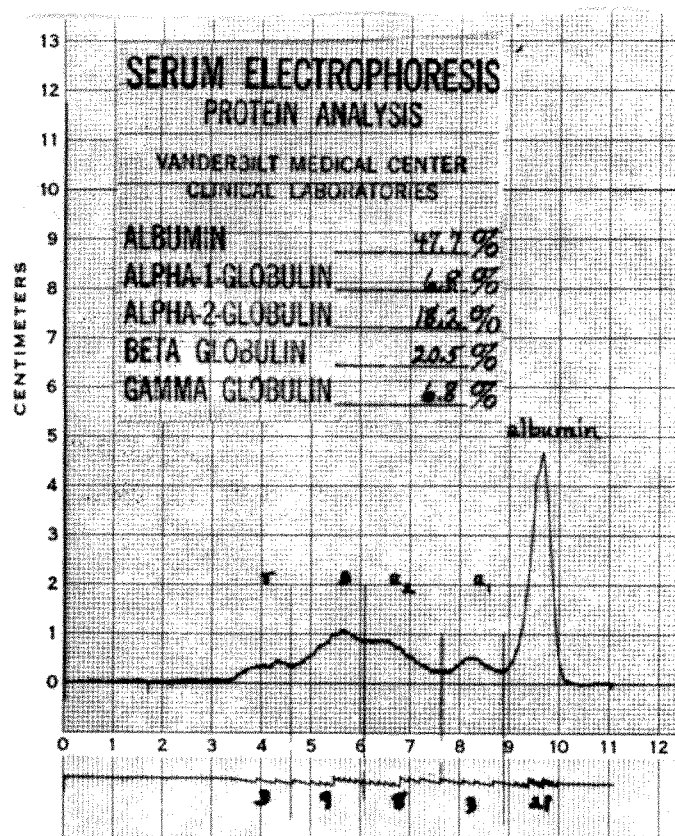


FIG. 1. Case 1 (N.B.) Serum protein electrophoretic pattern prior to operation. Total serum protein was 3.0 gm%; serum albumin was 1.8 gm%.

oral medication and intramuscular penicillin and streptomycin. The following day he complained of nausea and vomiting and was admitted to his local hospital. After several days of parenteral fluids, vomiting subsided but diarrhea continued and he noted facial and cervical edema progressing to involve his hands, legs and feet. There was a 15 pound weight gain. He was then referred to Vanderbilt University Hospital for further evaluation.

Past history included hay fever and wheezing each fall since childhood. The patient had complained of intermittent vague periumbilical discomfort for 9 or 10 years. This occasionally awakened him at night and was usually relieved by milk. System review was otherwise negative.

The family history was non-contributory.

Physical examination revealed a well-developed, well nourished, grossly edematous Caucasian man with normal vital signs. Temperature was 98.6, blood pressure 120/80, pulse 76, respirations 20. There was no generalized lymphadenopathy. Heart and lungs were normal. The abdomen was distended with a prominent fluid wave and no organs were palpable. There was 4+ pitting edema of the legs, the feet and the lower half of the trunk.

Initial laboratory studies showed normal urinalysis with no protein in numerous specimens. White blood count ranged from 9,400 to 14,750 with normal differential. Packed cell volume, icteric index, erythrocyte sedimentation rate and platelet counts were normal. Serum CO₂ was 34 mEq/l, chloride 88 mEq/l, sodium 130 mEq/l, potassium 4.6 mEq/l. These values returned rapidly to normal after hospitalization. Serum urea nitrogen, phosphorus, alkaline phosphatase, cephalin flocculation, thymol turbidity, uric acid, bilirubin, glucose, cholesterol, serological test for syphilis and anti-streptolysin-o titer were all normal. Prothrombin time was 87% normal. Serum protein bound iodine measured 3.8

mcg%; bromsulphthalein retention was 10% when the patient had severe edema with a serum glutamic oxaloacetic transaminase of 52 karmen units. D-xylose tolerance test was normal. Stool examinations were negative for blood, fat, ova and parasites.

The most striking laboratory abnormality was a total serum protein of 3.0 gm% with 1.8 gm% albumin. On multiple repeated determinations, albumin values ranged from 1.5 to 2.1 gm%. The serum protein electrophoretic pattern is shown in Fig. 1. Fasting gastric analysis showed free acid 12 degrees, total acid 27 degrees.

Electrocardiogram was normal as were x-ray examinations of the abdomen and colon. X-ray study of the chest showed a small loculated effusion in the right posterior pleural space. Upper gastro-intestinal x-ray series is shown in Fig. 2. Large folds of gastric mucosa were seen throughout the body and fundus of the stomach. These were most prominent along the greater curvature. Gastric flexibility and peristalsis were normal. Small bowel mucosa appeared slightly thickened but was otherwise normal. The radiologic impression was hypertrophic gastritis.

Gastroscopy showed "enlarged and bulbous folds" as well as "numerous 0.5 to 1 cm rounded papillomata throughout the lower body and angular areas of the stomach." Small ulcerated areas were seen on the tips of the papillomata. The flexibility and distention of the stomach again appeared normal. Per oral small bowel biopsy revealed normal jejunum with slender villi and normal stroma.

The patient was treated with a low salt, high protein diet and lost 29 pounds in 3 weeks. However, he continued to be nauseated, vomited intermittently and remained edematous.

Using standard isotope dilution techniques the patient's turnover rates, biological half-life and albumin pools were calculated after

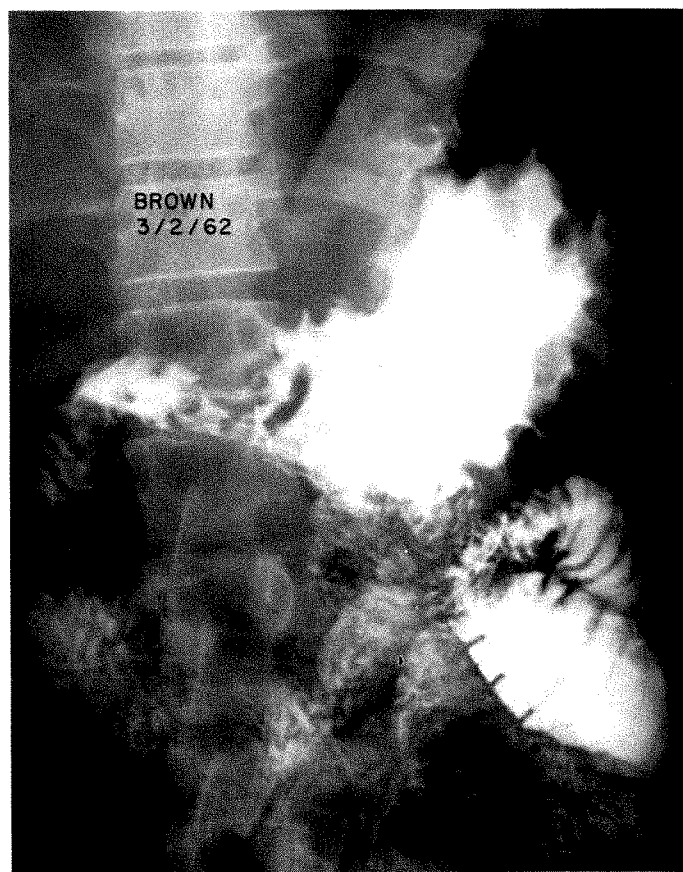


FIG. 2. Case 1 (N.B.) Upper gastrointestinal x-ray series before operation.

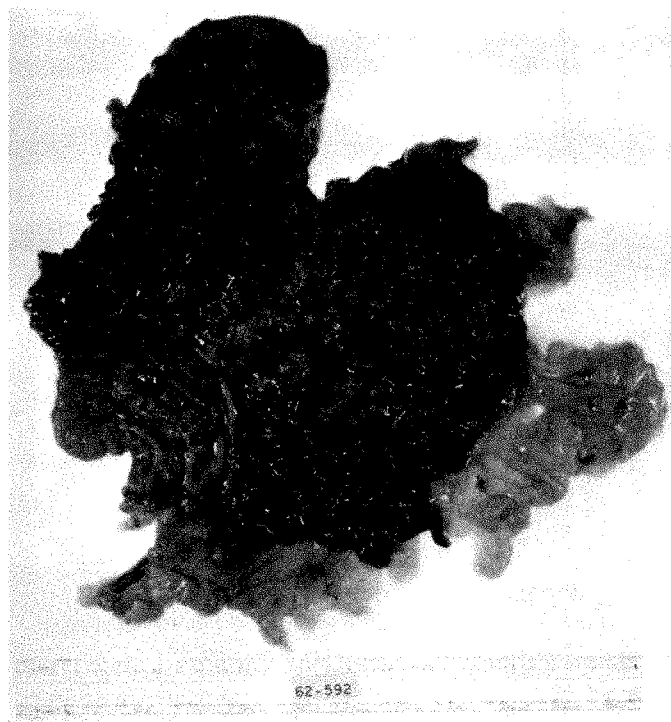


FIG. 3. Case 1 (N.B.) Photograph of resected stomach.

administration of ^{131}I labeled albumin.^{4,19} Total exchangeable albumin pool was 151.5 gms with a turnover rate of 16.5% and a daily degradation rate of 25 gms of albumin per day. The half-life of injected ^{131}I albumin was 4.2 days. Normal is 14-23 days.^{5,19}

The patient was discharged under treatment with an anabolic steroid

(Dianabol) as well as anticholinergic drugs and a phenothiazine to control nausea.

However, he returned to the hospital just three days after discharge complaining of uncontrollable nausea and vomiting.

Physical examination and laboratory data were as before with a following additional information: normal serum fibrinogen and urinary excretion of 0.16 grams protein per 24 hours. Two 12-hour overnight gastric secretion studies showed no free acid with large volumes of juice, 687 to 1644 cc's and total acid of 257 degrees in 1644 cc's. Gastric juice nitrogen content was 150 mg/100 ml (normal=52 mg/100 ml).

The patient was troubled by intermittent vomiting and diarrhea and continued to be edematous. A trial of gastric hypothermia was attempted while the patient was undergoing albumin turnover studies but he did not tolerate the procedure over a 10 hour period at 45° Fahrenheit outflow temperature.

Because of continued weight loss, anorexia, vomiting and persistent massive edema, nine units of albumin were administered intravenously in preparation for operation.

At laparotomy the most striking finding was the appearance of the stomach which was very thick walled with multiple areas of contraction and patterning which reflected the tremendous thickening of the gastric mucosa. Areas of plaque-like induration extended from the lesser curvature into the body of the stomach and thickening of the wall of the stomach extended from the cardia to the distal three inches of the organ. At this point there seemed to be a rather sharp line of demarcation between the greater thickened proximal stomach and the more normal feeling and appearing antral segment. The antrum, however,

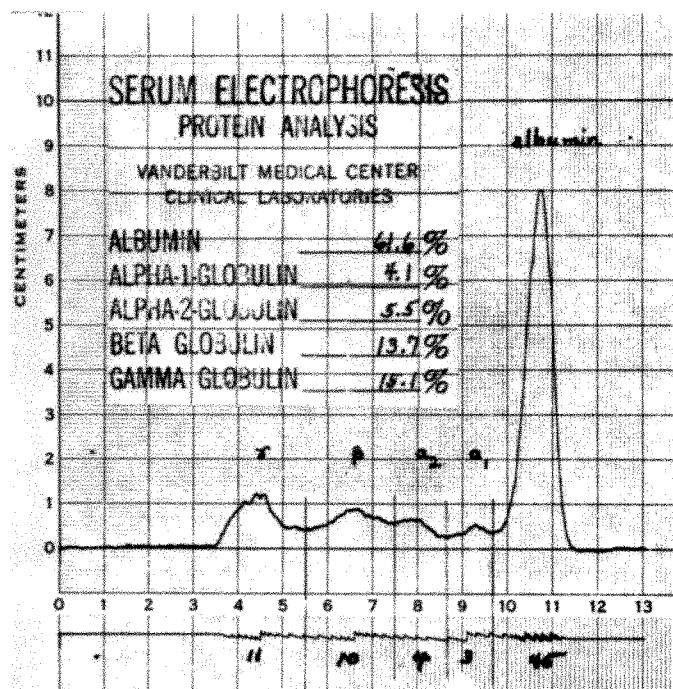
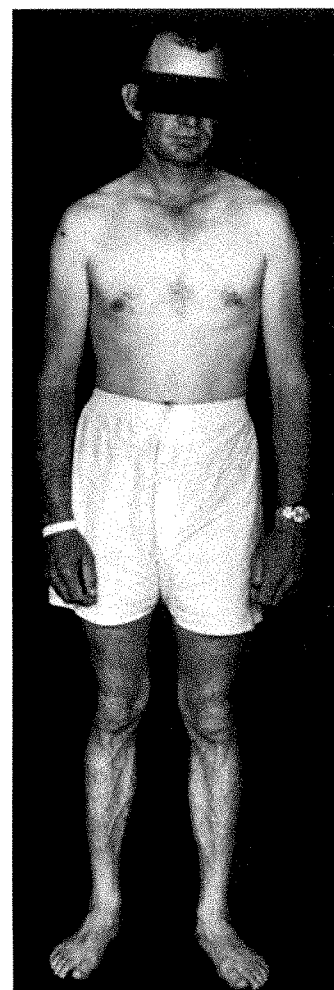


FIG. 4. Case 1 (N.B.) Serum protein electrophoretic pattern 10 years after total gastrectomy. Total serum protein was 7.5 gm%; serum albumin was 4.4 gm%.

FIG. 5. Case 1 (N.B.) Patient 10 years after total gastrectomy; weight 140 pounds.



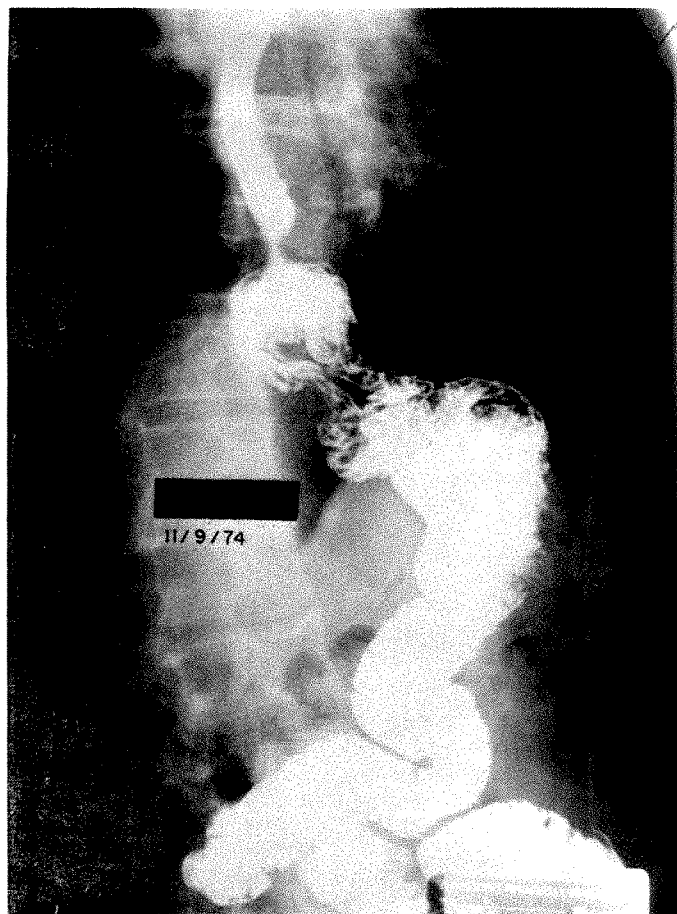


FIG. 6A. Case 1 (N.B.) Recent barium study of esophagus and Hunt-Lawrence jejunal pouch; esophagojejunal junction lies above diaphragm.

showed slight thickening and one could palpate individual folds of coarsened mucosa. There was no gross mass in the stomach to suggest a localized tumor. The nodes in the gastric mesentery were not enlarged. The spleen, however, was about twice normal size. On careful exploration, pancreas, duodenum, small and large bowel were normal. Because of the extensive involvement of the entire stomach in this process it was elected to perform a total gastrectomy with construction of a Hunt-Lawrence jejunal food pouch.²⁰

The patient tolerated the procedure well and made an uneventful recovery. Figure 4 shows postoperative serum protein electrophoretic pattern before discharge from the hospital. Postoperative albumin ¹³¹I half-life was 10.8 days. The patient tolerated postgastrectomy diet easily and well and was discharged on the eighteenth postoperative day.

Pathologic examination of the removed stomach was initially diagnosed hypertrophic gastritis. Figure 3 shows a photograph of the gross specimen. The gross and microscopic findings will be discussed in the text.

In the twelve years since the total gastrectomy the patient has had no further edema, has maintained a weight of 140 to 145 pounds and has returned to full time employment. His albumin turnover studies have remained normal and his only dietary limitations are avoidance of fluids with meals and avoidance of milk. Fig. 5 shows a recent postoperative photograph of the patient and Fig. 6 shows a recent barium study of the esophagus and the jejunal pouch.

During this twelve year period the patient's nutrition has been satisfactory. He has been maintained on vitamin B₁₂, 500 micrograms IM, every 6 weeks. Recent blood studies showed his hemoglobin 13.8 grams

%, packed cell volume 43%, MCHC 31.8, total serum protein 7.5 grams%, serum vitamin A 67 µg%, vitamin C 1.5 mg%, vitamin E 0.8 mg%, vitamin B₁₂ 355 µgms/ml, serum folate 12.4 ng/ml, serum albumin 4.4 gms%.

L.D., a 26-year-old Negro woman was admitted to Vanderbilt University Hospital in March, 1962 complaining of nausea, vomiting, diarrhea and abdominal pain.

Present Illness. Four weeks prior to admission the patient noted "indigestion" at first relieved by antacids but progressing to constant burning, epigastric pain and vomiting. These symptoms persisted and one week later she developed diarrhea and ankle edema and was hospitalized elsewhere for one week. Continuous vomiting and mild diarrhea (two to three blood-free, loose watery stools per day) persisted and the patient was transferred to a second hospital (Hubbard).

Physical examination on admission to the Hubbard Hospital showed her to be a thin young woman who weighed 106 pounds with a slightly puffy appearance and edematous extremities. The only positive physical finding was presence of a 2 cm firm thickening in the left lobe of the thyroid and pitting pretibial edema. Pertinent laboratory data showed the hemoglobin to be 16.5 gms% with a packed cell volume of 46%. Total serum protein was 3.8 gms% with an albumin of 1.7 gms% and globulin of 2.1 gms%. X-ray studies of the upper gastrointestinal tract showed a marked irregularity of the contour and mucosal pattern in the entire stomach with giant hypertrophy of the gastric rugae extending from the cardia and fundus down to the incisura angularis. The walls of



FIG. 6B. Closer view of site of esophagojejunal junction.

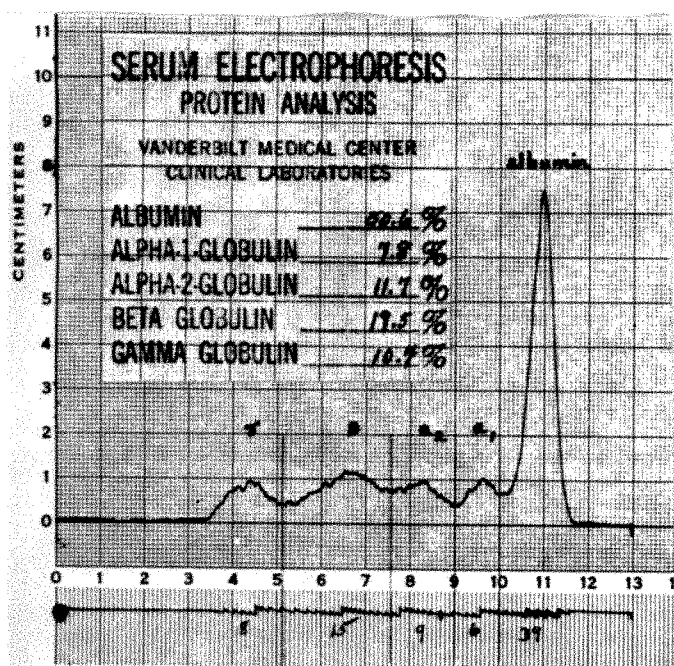


FIG. 7. Case 2 (L.D.) Serum electrophoretic pattern on admission to hospital (V.U.H.). Total serum protein (after treatment started) was 4.7 gm%; albumin was 2.8 gm%.

the stomach were flexible throughout although peristaltic activity was somewhat diminished. The roentgenologist suspected lymphomatous involvement of the stomach or extensive granulomata.

On March 9, 1962, exploratory laparotomy was performed by Dr. Matthew Walker who found large, soft gastric mucosal folds in the stomach which could be readily palpated from the exterior. On gastrotomy the mucosa in the antral region seemed to be normal, while the mucosa of the body and fundus showed extensive hypertrophy with giant rugae extending from the cardia into the stomach down to the antrum. A small segment of the gastric wall was removed for biopsy and a feeding jejunostomy was established.

The patient made a satisfactory recovery from operation and was started on high protein jejunostomy feedings in the early postoperative period. Gastric analysis during this time showed no free acidity with a total acidity of 6.3 degrees. The gastric juice contained 1.4 grams of protein per 100 ml. Despite the high protein jejunostomy feedings, hypoproteinemia and hypoalbuminemia persisted and she was transferred to Vanderbilt University Hospital for further study. The patient had lost approximately fifteen pounds during this illness.

Past history and family history were non-contributory.

Physical examination on admission to Vanderbilt University Hospital revealed a slender, asthenic Negro woman with normal vital signs except for a sinus tachycardia of 120 per minute. Significant findings included a slightly enlarged left lobe of the thyroid and a well healed laparotomy incision with a jejunostomy catheter in place. There was 1+ pitting edema of the pretibial area bilaterally.

Laboratory data included a normal urinalysis with no proteinuria. White blood count was 22,000 on admission and ranged from 16,200 to 35,000 with a predominance of polymorphonuclear cells and a slight shift to the left with up to 12% band forms. Packed cell volume was 41% on admission but over a 4 day period fell to 23%. Erythrocyte sedimentation rate was 12 mm/hour.

Serum urea nitrogen was 27 mg%, CO_2 16.5 mEq/l, chloride 84 mEq/l, sodium 124 mEq/l and potassium 3.8 mEq/l. These findings reverted to normal with parenteral alimentation; however, she maintained an elevation of serum urea nitrogen of 21 to 42 mg% throughout her course.

Additional studies included alkaline phosphatase 5-9 Bodansky units, serum glutamic oxaloacetic transaminase 44-111 Karmen units and serum glutamic pyruvic transaminase 430-230 Karmen units. Total serum protein was 4.7 grams% with 2.8 grams% albumin and 1.9 grams% globulin. The serum protein electrophoretic pattern is seen in Fig. 7. Serum cholesterol was 205 mg%, bilirubin was 3 mg% with 1.2 mg% direct fraction. B.M.R. was +10%. Protein bound iodine was 7 $\mu\text{g}\%$.

An electrocardiogram was interpreted as normal with a sinus tachycardia. X-ray examination of the chest and abdomen were unremarkable on admission. Subsequent studies of the upper gastrointestinal tract with gastrographin showed large gastric mucosal folds and mild partial obstruction in the region of the third portion of the duodenum.

During her stay in the hospital repeated 24 hour gastric aspirations revealed volumes of 2880, 2850, 1000 and 1855 ml with 3 to 5 degrees free acid, 35 degrees to 60 degrees total acid and pH of 6.6 to 6.85. Total gastric juice nitrogen was 140 mg/100 ml to 144 mg/100ml or 4.1 to 5.4 gms/24 hours. ^{131}I labeled albumin studies were carried out to measure biologic half-life and albumin turnover rate but counting errors disqualified the data.

During hospitalization the vomiting continued and feedings were attempted by mouth or by jejunostomy. A diagnosis of partial intestinal obstruction was made. Gastric suction and fluid replacement resulted in moderate improvement. After hydration her packed cell volume fell to anemic levels (23%) with no evidence of blood loss. Two units of blood were given.

Two days later while reoperation was under consideration, the patient suddenly went into ventricular fibrillation. Immediate external cardiac massage and defibrillation were carried out but were unsuccessful. Thoracotomy with massage and defibrillation was added but proved to be of no avail and the patient was pronounced dead. On the day of death her serum electrolyte levels were within normal limits except for a potassium of 5.5 mEq/l and a CO_2 of 17 mEq/l.

Autopsy examination failed to show a satisfactory explanation for the immediate cause of death. There was decreased turgor and dryness of tissues suggesting dehydration at the time of death. The thyroid showed no abnormality except for a 1 cm cyst in the left lobe. The heart showed no anatomic abnormality. The gastric mucosa showed marked hyperplasia and hypersecretion of the mucous neck cells with total absence of parietal and zymogenic cells in the body and fundus with a quite severe, acute inflammatory reaction. The large folds did not involve the antrum (Fig. 8). The mucosa over the giant rugal folds was 5 to 7 mm in thickness. There was no definite point of obstruction in the

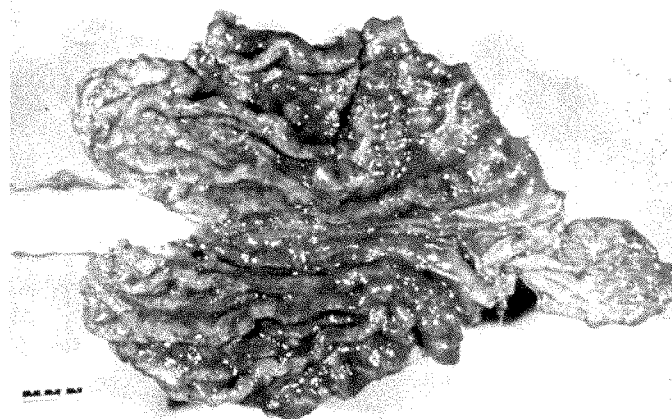


FIG. 8A. Case 2 (L.D.) Photograph of stomach taken at autopsy. The hypertrophied mucosal folds occupy body, cardia and fundus.

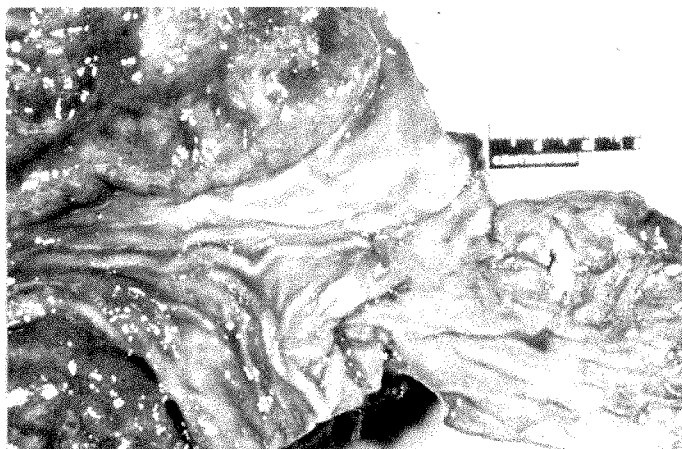


FIG. 8B. Closer view shows the small antrum is not involved.

duodenum, jejunum or any other portion of the gastrointestinal tract. Gross and microscopic examination of the remaining organs showed normal findings. The pathologic diagnosis was Menetrier's disease with protein-losing gastroenteropathy.

F.B., a 33-year-old Caucasian man, was admitted to the Vanderbilt Hospital in January, 1974 complaining of severe generalized abdominal pain of two hours duration.

Present Illness. The patient had had three previous admissions to the Vanderbilt Hospital over the previous 2 years because of persistent epigastric burning pain of 6 years' duration with 3 episodes of upper gastrointestinal bleeding. The pain was consistently described as burning and crampy, made worse by prolonged periods of fasting or eating spicy foods.

At his first admission in November, 1972, there were no unusual findings on physical examination but laboratory studies showed him to have total serum protein of 5 gms% with albumin of 3.2 gms%. A battery of additional laboratory studies were in the normal range and upper G.I. series showed giant gastric folds in the body and fundus of the stomach with the antrum appearing relatively normal. No ulcerations were identified. A diagnosis of Menetrier's disease was suggested with the differential diagnosis of lymphoma to be excluded. Gastroscopic examination confirmed the presence of the giant rugal folds in the body and fundus of the stomach while the antrum and pylorus appeared to be entirely normal. The first 15 cm of duodenum appeared to be entirely normal. No definite site of ulceration or explanation for bleeding was identified. Biopsies of the hypertrophied mucosa were obtained. The patient was discharged on a bland diet but returned with recurrent gastrointestinal bleeding episodes and was readmitted in March, 1973 with similar findings and then again in November, 1973 with identical findings. On each of these occasions bleeding stopped spontaneously and repeat upper G.I. and gastroscopic studies confirmed the presence of the giant gastric rugal folds but failed to demonstrate a specific bleeding point (Fig. 9). At the third admission, four units of blood were transfused. At each of these admissions, the hypoproteinemia and hypoalbuminemia were confirmed. Biopsies of the gastric mucosa showed superficial acute and chronic inflammatory changes but no specific diagnosis could be made. In the November, 1973 admission, aortography was done with selective celiac and superior mesenteric arteriograms (Fig. 10). These studies confirmed the presence of the giant hypertrophic gastric rugae with a large submucosal venous channel underlying these but no varices or active bleeding sites were identified. Gastric analysis showed no titratable acid in a 55 cc fasting specimen with pH 7.08. There was a normal response in acid secretion to histamine (histalog) stimulation.

After the bleeding had stopped a ^{51}Cr labeled albumin study was

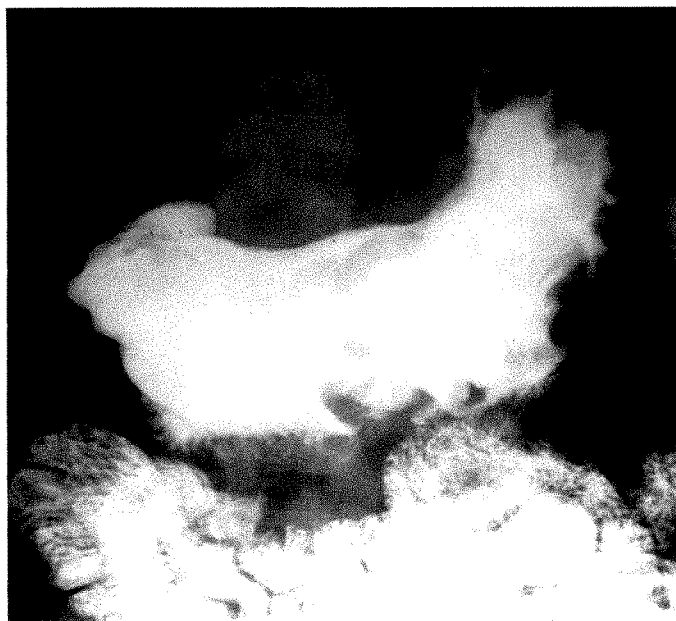


FIG. 9A. Case 3 (F.B.) Upper gastrointestinal x-ray series showing giant rugal folds in body, cardia and fundus of stomach.

carried out which showed loss of 53% of the labeled albumin in 96 hours (normal loss should be less than 2%). After discharge from this third admission the patient was maintained on a bland diet which he followed but with persistence of epigastric burning pain. Two hours before his fourth admission his epigastric pain became excruciatingly severe and generalized.

Physical examination in the Emergency Service at the Vanderbilt University Hospital showed him to be acutely ill with severe abdominal

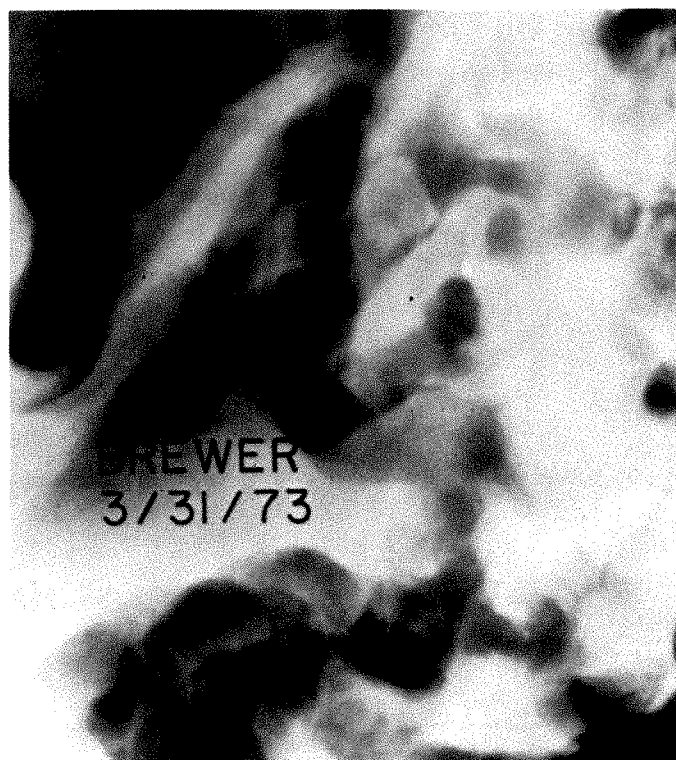
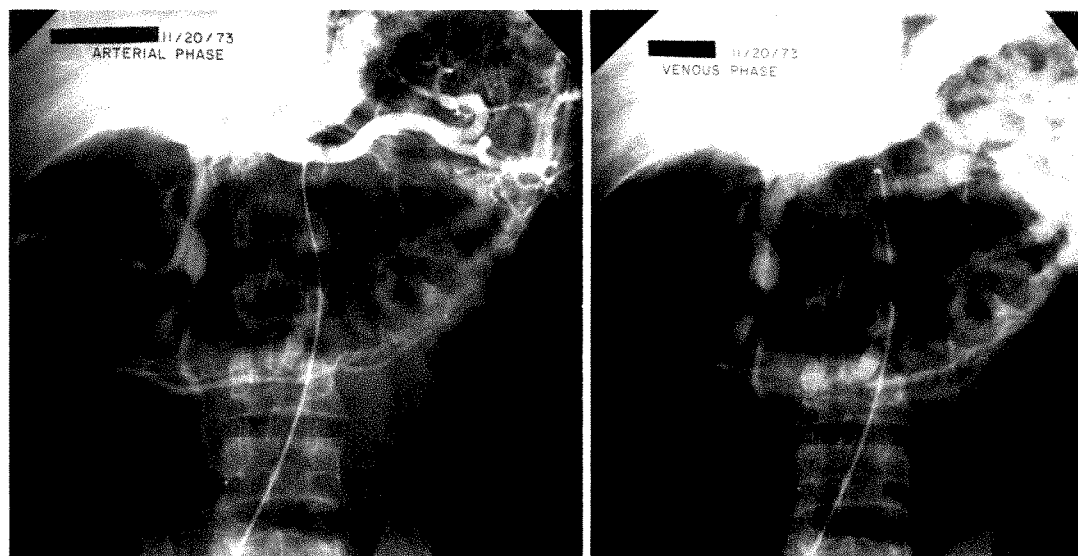


FIG. 9B. Closer view of upper G.I.

FIG. 10. Case 3 (F.B.) Selective celiac arteriogram. Hypertrophied gastric rugae are seen. No definite bleeding site was identified (left) in either arterial or (right) venous phases. Large submucosal veins are seen in venous phase.



tain. Temperature was 97.4, pulse 104, respirations 20, blood pressure 20/60. Examination of the abdomen showed him to have diffuse generalized tenderness to palpation with rigid abdominal musculature. Bowel sounds were absent. The remainder of the physical findings were not remarkable. There was no ankle or pedal edema. A diagnosis of Menetrier's disease with protein-losing gastropathy and perforated peptic ulcer was made.

The patient was taken immediately to the operating room where this diagnosis was confirmed. There was a 4 mm perforation of a gastric ulcer located high on the lesser curvature about an inch below the esophagogastric junction. There was a large area of induration 2 to 3 inches in diameter surrounding this perforation. The upper portion of the stomach was massively thick-walled with great thickening of the mucosa involving the body and fundus. The antrum seemed to be relatively free of this process. There was no localized tumor mass in the stomach except for the area of induration surrounding the perforated ulcer. A biopsy of the gastric wall confirmed the diagnosis of Menetrier's disease. Total gastric resection was then carried out and alimentary reconstruction accomplished by Roux-en-Y esophagojejunostomy with construction of a Hunt-Lawrence jejunal pouch.²⁰

The patient withstood his procedure well. On the second day after operation he was started on parenteral hyperalimentation. This was

maintained until the second postoperative week at which time he took postgastrectomy diet well. His wound healed per primam and he made an uncomplicated recovery. He was discharged on the twelfth postoperative day.

Pathologic examination of the removed stomach confirmed the diagnosis of Menetrier's disease with the perforated gastric ulcer. The giant rugal folds in the formalin fixed specimen are shown in Fig. 11.

The patient has been followed for 11 months during which time he has

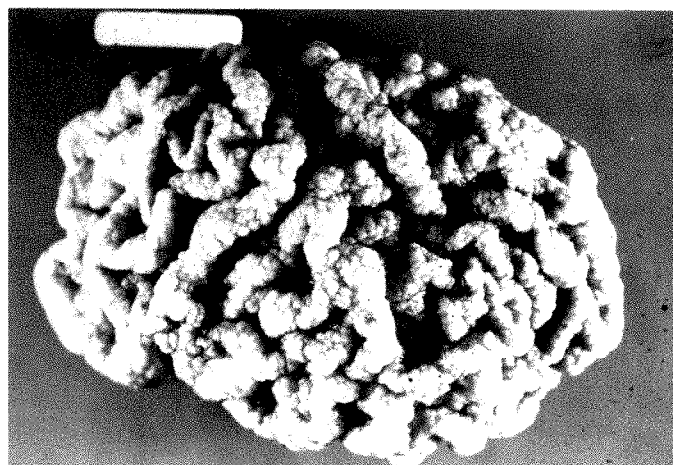


FIG. 11. Case 3 (F.B.) Giant rugal folds in opened, formalin fixed specimen resemble convolutions of the brain.



FIG. 12. Case 3 (F.B.) Barium study of esophagojejunal anastomosis and Hunt-Lawrence jejunal pouch shortly after operation.



FIG. 13. Case 3 (F.B.) Photograph of patient taken 11 months after total gastrectomy with Roux-en-Y esophagojejunostomy and Hunt-Lawrence jejunal pouch. Weight 139 pounds.

been relieved of epigastric pain. He has a normal food capacity but abstains from consuming fluids with meals and avoids milk; otherwise, he eats an unrestricted diet. A barium study of the esophagojejunal reconstruction with jejunal pouch done shortly after operation is shown in Fig. 12. Fig. 13 is a recent photograph of the patient. His weight has been maintained at 138 to 140 pounds. He is 5 feet, 9 inches tall. He has worked regularly as an automotive service worker.

He has received 500 μg of vitamin B₁₂ every 6 weeks intramuscularly. Recent serum vitamin levels were: B₁₂ 280 $\mu\text{g}/\text{ml}$; A 68 $\mu\text{g}\%$; C 3.4 $\text{mg}\%$; E 0.7 $\text{mg}\%$; folate 16.7 ng/ml . Total serum protein was 7.2 $\text{gms}\%$; albumin 4.5 $\text{gms}\%$. Repeat ⁵¹Cr labeled albumin measurement of gastrointestinal protein loss showed less than 2% loss of the labeled albumin in 96 hours (normal loss should be less than 2%).

Pathologic Anatomy

The entire stomach of each patient was available for examination and each revealed a remarkable increase in mucosal mass which was thrown into rich folds and smaller nodules, forcing the muscularis mucosae into peak-like prolongations supporting the increase in mucosa. In each case, the mucosa measured up to 6-8 mm in height and occasionally the valleys between the giant infoldings

of mucosa measured 2-3 cm in depth. (Figs. 3, 8, 11 and 14). In each case these notable changes were confined to the regions of fundus and body which contain gastric glands and spared the antral region.

Histologically, the antral region also appeared within normal limits with remarkable changes confined to the gastric glands of the fundus and corpus. Although major histologic differences were demonstrated among the three cases, the unifying feature was a complete absence of identifiable parietal and chief cells which normally compose the gastric glands. Instead, this rich epithelium was composed of simple mucus-secreting cells of the type seen in the neck region of the normal gastric glands and which contain primarily neutral muco-substances and thus stain richly with the periodic acid Schiff stain. Case 3 (F.B.) demonstrated the most extreme degree of mucosal hypertrophy with a mild degree of inflammatory infiltrate in the intervening connective tissue but did have a massive degree of interstitial edema and demonstrable dilatation of lymphatic channels in the submucosa, subserosa and regional lymph nodes. This case was also unique in that two small ulcers were present along the lesser curvature: one of these measured 8 x 4 mm and was well healed, extending into but not through the muscular coat and was present in the region of antral glands. Just proximal to the demarcation between corpus and antral glands along the lesser curvature was an area of hemorrhagic and edematous mucosa which had a tiny, centrally placed, acute perforated ulcer of 1-2 mm which extended through the entire muscular coat and serosa of the mid lesser curvature and was associated with a small amount of acute inflammatory exudate around the serosal opening.

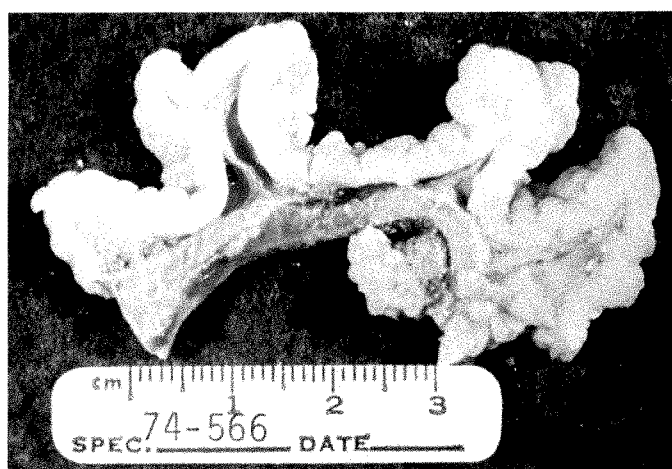


FIG. 14. Photograph of a cross-section of gastric body from Case 3 (F.B.). The muscularis propria presents a curvilinear configuration at the lower part of the picture. The mucosa appears as cobblestones covering a submucosa which is drawn up into four folds by the increase in mucosal surface. A mucosal thickness of 5 mm is demonstrated after fixation in buffered formalin.

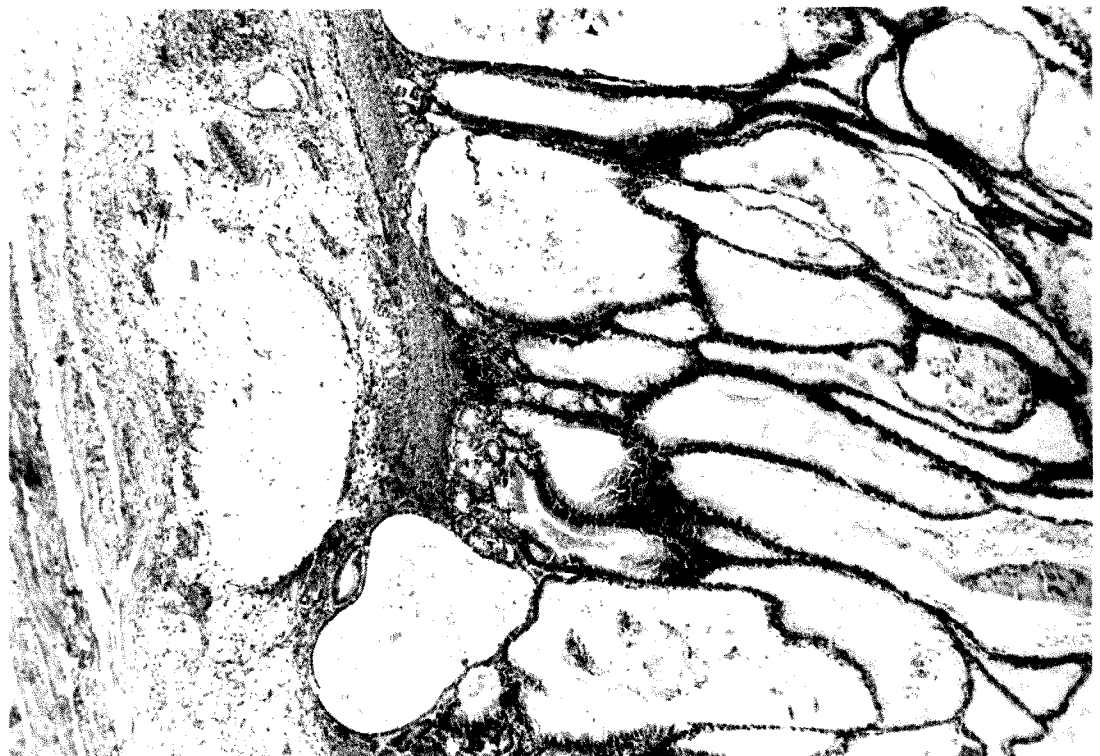
FIG. 15. Case 1 (N.B.) Histologic section of gastric body, Hematoxylin and Eosin (x85). Muscularis mucosae crosses lower portion of photograph with simple, mucus-secreting glands above.



Case 1 (N.B.) differed only slightly in appearance with no ulceration, presenting a stomach measuring almost precisely the same as Case 3 (32 cm along the greater curvature and 14-16 cm along the lesser curvature). Many

of the mucosal-lined abnormal glands were cystically dilated (Fig. 15) and had varying amounts of inflammatory cells, predominantly polymorphonuclear leucocytes, in the cystic spaces. Occasional lymphatics and venules of

FIG. 16. Case 2 (L.D.) Histologic section of gastric body, Hematoxylin and Eosin (x21). Muscularis mucosae in lower third of photograph is separated by two large mucus lakes, the larger one of which lacks a complete mucosal covering.



the submucosa contained deposits of fibrin and fresh thrombi. A marked interstitial edema was also present at occasional sites.

Case 2 (L.D.) demonstrated the least degree of mucosal increase in mass leaving a definite impression that it was in a stage of atrophy with many mucus cells appearing flattened with little cytoplasm. Chronic inflammatory cells were much more marked, and unique to this case was the extension of mucus secreting glands and pools of mucus into the muscularis mucosae in many sites (Fig. 16).

Etiology and Pathophysiology

The cause of this condition is unknown. Many hypotheses have been presented including the possibility that it represents a congenital anomaly or the effects of chemical, thermal or mechanical irritants or infectious agents.^{3,10,22} The possibility that it represents an autoimmune mechanism has been suggested.⁶ There is little or no substantial evidence to support these ideas of etiology.

The restriction of the giant mucosal hypertrophy to the fundus, cardia and body of the stomach, sparing the antrum, is reminiscent of the Zollinger-Ellison syndrome and suggests an endocrine cause for Menetrier's disease. The enormous mucosal hyperplasia and hypertrophy in the Zollinger-Ellison syndrome reflects a response of the parietal and chief cells to gastrin produced by the endocrine tumor.²⁴ In Menetrier's disease the giant mucosal hypertrophy and hyperplasia consists almost exclusively of gastric mucus cells. Parietal and chief cells are notably diminished in number and indeed are absent in many sections.

Although the body of literature concerning hypertrophic gastritis and giant gastric rugal folds has been burdened by a great degree of terminologic proliferation and nosologic confusion, it seems that since about 1960 a general agreement has been approached.^{17,22} The diagnosis "Menetrier's disease" is now usually confined to those cases of giant hypertrophic gastropathy in which basal acid secretion is low or absent and serum proteins are commonly lost from the mucosal surface. Stempien and his associates²² emphasized that Menetrier's disease "is at the opposite end of the spectrum of the hypertrophic gastropathies from that of hypertrophic hypersecretory gastropathy." The latter entity includes the Zollinger-Ellison syndrome with its spectrum of high acid secretory clinical manifestations including intractable peptic ulcer disease and an association with multiple endocrine adenomatosis. As Stempien²² pointed out 10 years ago, the hypertrophic hypersecretory gastropathies are characterized by hypersecretion of HCL, pepsin and mucoprotein. No significant serum protein losses occur into the gastric juice. The mucosal hypertrophy involves

all glandular elements, parietal cells, chief cells and mucus cells. On the contrary, Menetrier's disease is characterized by mucosal hypertrophy associated with degenerative changes in the glandular layer, a hyperplasia involving superficial epithelium and remnants of the glandular layer, an acidity or marked hypo-acidity and significant losses of serum protein into the gastric juice. Gastric ulceration is rare in association with Menetrier's disease, but has been reported.^{12,14} The persistent peptic ulcer symptoms coupled with recurrent upper gastrointestinal bleeding episodes and finally with perforation of a gastric ulcer as occurred in our third patient (Case 3, F.B.) emphasizes this potential relationship. A widely varying amount of inflammatory interstitial change and edema has been described in reported cases and was present in our patients. These changes evidently add to the great increase in mucosal mass. Their etiology is unknown but it has been pointed out by Frank and Kern⁶ that this process may proceed to atrophy and indeed the gastric mucosa in our second patient (Case 2, L.D.) seemed to be in process of developing such an alteration.

Hypoproteinemia with Menetrier's disease was first shown by Citrin, et al.⁴ in 1957 to be associated with loss of serum proteins across the gastric mucosal barrier into the gastric lumen. This was established by injecting radioactive albumin intravenously and recovering excessive amounts of labeled protein in the gastric juice of their patient. The implication of these early studies was that the protein losses consisted mostly of albumin which resulted in low serum protein values. However, Katzka et al.,⁸ in 1967 pointed out that patients with Menetrier's disease with protein losses had low serum globulin concentrations as well as hypoalbuminemia. In addition, he cited the work of Glass⁷ who reported that paper electrophoretic curves of gastric juice in Menetrier's disease show a large globulin peak as well as a large albumin peak. Katzka⁸ had similar findings in his patient with Menetrier's disease using starch block electrophoretograms. Gastric juice protein in 41 normal patients studied by Katzka⁸ averaged 1.7 mg/ml. In his patient with Menetrier's disease gastric juice protein was 8 mg/ml and 8.8 mg/ml on two separate occasions. A similar range was found in the gastric juice of our 3 patients. In the series of 18 patients with protein losing gastroenteropathy reported by Schwartz and Jarnum¹⁹ in 1961, the hypoproteinemia could be explained in all by excess gastrointestinal protein loss demonstrated by an increased fecal excretion of radioactivity following intravenous injection of ¹³¹I labeled albumin and/or ¹³¹I labeled polyvinylpyrrolidone.

In Menetrier's disease the exact mechanism of transport of serum proteins across the gastric mucosal barrier into the lumen of the stomach is not known. However, digestion of the proteins by proteolytic enzymes must

take place with reabsorption of the constituent peptides and aminoacids to an unknown extent while the remainder of these constituents is lost in the stool. Citrin et al.⁴ found that their patient with Menetrier's disease had a small exchangeable albumin pool which was turning over rapidly. From their study they concluded that the capacity of the body to synthesize albumin was inadequate to compensate for the gastric losses despite the availability of the constituent aminoacids of the albumin in the intestine. They thought that this was the probable pathogenesis of the hypoalbuminemia and the diminished total pool in their patient.

Clinical Aspects

In the 1962 review of Reese, Hodgson and Dockerty,¹⁵ the authors stated that only 80 cases of Menetrier's disease, verified pathologically, had been reported by 1960. According to Raotma et al.¹⁴ in 1974 only about 200 cases of Menetrier's disease have been reported since the original description in 1888. If the criteria used for the diagnosis are those listed in the previous section, Raotma's¹⁴ estimate of the frequency of Menetrier's disease should be reduced considerably. Reese and his associates¹⁵ used the radiologic criteria for diagnosis of Menetrier's disease developed in their retrospective review of the subject and found only 18 patients at Mayo Clinic during the period 1949-1960 who met all the criteria and in whom pathologic material was available. These 18 patients had total or subtotal gastrectomies and in only 6 of this group was the pathologic diagnosis of Menetrier's disease confirmed. The 12 other patients had tumors, principally carcinoma or lymphoma, gastric ulcers, antral spasm or retained secretions which mimicked Menetrier's disease. Thus, the true incidence of Menetrier's disease is difficult to determine from reports in the literature, but we believe it to be much less common than the literature would suggest.

According to Spiro,²¹ patients with Menetrier's disease may present with massive edema, with gastrointestinal bleeding, or with non-specific gastrointestinal complaints which have often led to a roentgenographic diagnosis of gastric lymphoma or carcinoma. In our patients edema and hypoproteinemia were the chief complaints in one patient, nausea, vomiting and diarrhea in another, while the third clearly had persistent peptic ulcer symptoms with recurrent bleeding and eventually perforation.

The disease appears to be an acquired disorder and the clinical manifestations may develop rapidly in a few weeks as in two of our patients or may evolve more slowly and persist over a period of years (as in Case 3). Once it develops in adults, Menetrier's disease with protein-losing manifestations seems to be persistent and unrelenting with a highly lethal course when untreated.

In children several reports indicate that a protein-losing gastropathy with giant gastric rugae which resembles Menetrier's disease may develop and, after a period of weeks of supportive treatment, undergo spontaneous remission.^{2,13,16}

Radiologic study of adult patients with Menetrier's disease shows the presence of long tortuous gastric rugal folds which are frequently one to two centimeters in thickness on examination with barium, separated by deep sulci of equal depths. The criteria originally delineated by Reese et al.¹⁵ in 1962 for radiologic diagnosis of the disease emphasized that the folds are concentrated in the fundus, cardia and body of the stomach and end at the incisura angularis, sparing the antrum. Air contrast studies may improve the detail of examination. Fluoroscopes accompanied by palpation and compression of the stomach often demonstrates the enlarged folds to best advantage. The configuration of the greater curvature, according to Reese et al.,¹⁵ is quite characteristic since barium insinuates itself between the enlarged folds and forms coarse septal lines. Even when the giant rugae cannot be seen a rough estimate of their height can be determined by measuring the perpendicular lines on the greater curvature which represent spicules of barium trapped by opposed folds. The lesser curvature is frequently spared in this process. The thickness of the gastric wall is often 10 mm or more and the enlarged rugal folds are characteristically quite flexible. Lymphoma and carcinoma can be differentiated when localized masses of tumor are present, when the gastric wall is inflexible at the site of neoplastic infiltration and when the distal portions of the stomach are involved by tumor. Zollinger-Ellison syndrome can simulate Menetrier's disease but large duodenal folds and the presence of duodenal ulcer, single or multiple, aid in the differential.

Gastroscopy can be very helpful in diagnosis by confirming the presence and flexibility of the large rugal folds and the absence of antral involvement. Persistence of the folds under distention with air helps to distinguish them from the occasionally normal folds which look large radiologically.²¹ While gastroscopic biopsy in multiple areas should be carried out, the thickness of the gastric wall in Menetrier's disease often precludes a definitive diagnosis on the superficial bit of tissue obtained by gastroscope. Biopsy, however, is exceedingly helpful in identifying or excluding neoplasms which must be differentiated.

Laboratory studies which contribute to the diagnosis of Menetrier's disease include measurement of gastric acid secretion which is usually absent or in the hypochlorhydric range. This helps to differentiate the disease from hypertrophic, hypersecretory gastropathy²² including the Zollinger-Ellison syndrome where acid secretion is usually in the upper normal or excessively high ranges. As advocated by Katzka⁸ measurement of pro-

tein in gastric secretion, electrophoretically or chemically, characteristically shows elevated protein concentrations in the juice of patients with Menetrier's disease and can reach concentrations of 8 to 9 mg/ml as contrasted to a normal level of 1.7 mg/ml. The protein losing syndrome accompanying Menetrier's disease can readily be recognized by subnormal levels of both albumin and globulin in the patient's serum, as occurred in each of our 3 patients. Confirmation of diagnosis of the protein losing syndrome can be elaborated by the use of ^{131}I labeled albumin or ^{51}Cr labeled albumin to demonstrate the accelerated turnover of exchangeable albumin, its loss in gastric juice and of its isotopic marker in stool and urine.

Treatment of Menetrier's disease with protein-losing gastropathy has obviously developed by empiricism. Since the etiology of the disease is unknown, there is no specific therapy. Therapeutic trial of a variety of drugs, including steroids, high protein diets, repeated infusions of albumin and gastric irradiation have proven totally inadequate when the clinical manifestations of Menetrier's disease and the protein losing syndrome are severe.⁹ Under such circumstances the gastric protein losses must be curtailed and resection of the site of protein loss is a logical and effective treatment. Since the hypertrophied gastric folds which are the site of protein loss occupy the fundus, cardia and body of the stomach and only the small antrum might theoretically be spared when a curative gastric resection is done, we believe that total gastrectomy with the several advantages of Roux-en-Y esophagojejunostomy and a jejunal food pouch²⁰ is preferable to an alternative reconstruction designed to retain the antrum. We have used the Hunt-Lawrence²⁰ type of jejunal pouch in our two surgically treated patients with elimination of the manifestations of Menetrier's disease and good rehabilitative results.

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DISCUSSION

PROFESSOR J. PHILIP SANDBLOM (Lausanne, Switzerland): It is interesting to speculate on other types of lesions in the gastrointestinal tract with great losses of protein and water. A couple of years ago I was confronted with a very unusual case; in fact, I have never seen any other such described. It was given to me by Professor Caroli in Paris, because it was a case of hemobilia, caused, as he thought, by polyposis in the biliary tract.

(Slide) This patient had pronounced hemobilia. The operative cholangiogram showed multiple polyps in the biliary tract. Professor Caroli could only scoop out a few of these.

The characteristic thing for this patient was a tremendous loss of fluid, electrolytes and protein, and the patient died after three or four days, having lost between 10 and 15 L a day of protein-rich fluid through the T-tube. This case, I think, rather resembles the Menetrier's syndrome; and I wonder if they are related.

One also thinks of the hypersecreting villous adenomas of the colon,

which may produce tremendous loss of water, electrolytes and protein, and can give the same hypoproteinemia as Menetrier's disease.

When discussing this with Dr. Walter Ballinger just before the meeting, he suggested that perhaps there is something else than just the local changes which is the cause of this—some kind of a hormonal disturbance. It is tempting to think that in both villous adenoma, in the Menetrier's disease and in the case I described there is production of some hormone that produces the terrific loss of water and protein. The success with resection might be due either because one has removed the production place, or the trigger mechanism for this unknown hormone.

DR. H. WILLIAM SCOTT, JR. (Closing discussion): We believe this disease should be an endocrinopathy, but we don't know quite what endocrine system is involved. It appears to be a disorder which perhaps

might be explained by suppression of gastrin. Sadly enough, we have no gastrin data in any of our patients.

I talked to Dr. James Thompson shortly before this meeting, asking him if he had had the opportunity to measure serum gastrin in any such patient, and he has not; so if anyone has an opportunity to see one of these patients, certainly it would be interesting to find out whether there is an abnormality of gastrin.

The disappearance of the parietal cells and the overgrowth of the mucus cells in these great hypertrophied mucous folds certainly suggest some kind of tropic mechanism that is driving the parietal cells away and producing overgrowth of mucus producing cells; but what on earth that could be I have no idea. It's a condition—a disorder—which is looking for a tropic hormone to explain it, I think, and someone ought to be able to find the answer by looking in that direction.

Blood Transfusions in Elective Operations: Comparison of Whole Blood versus Packed Red Cells

HOWARD D. ROBERTSON, M.D., HIRAM C. POLK, JR., M.D.

For some years the use of packed red cells in elective operations has been encouraged on an empirical basis. From the clinical and laboratory information gathered in this prospective, randomized, but unblinded study of 294 patients subjected to elective general, thoracic, or gynecologic operations, the use of packed cells in such situations appears rational. Such practices minimize demand upon a unique human resource, may give patients fewer undesirable elements in blood transfusions, and do not increase the morbidity or mortality of patients receiving transfusion.

BLOOD TRANSFUSION is a common and important component of medical therapeutics. Particularly frequent are transfusions done coincident to elective operations. Although often taken for granted, transfusion has allowed important advances in elective surgery. In one multi-decade study of colon surgery in two medical centers, a precipitous decline in operative mortality coincided precisely with the institution of blood banks in the late 1930's in the respective institutions.⁸ Further improvements in anesthesia and surgical and supportive techniques have allowed and will continue to allow more difficult operative procedures, with escalating demand for even more blood resources.

The use of blood no doubt should be as specific as with other forms of therapy. Blood component therapy, as now advocated, uses each cellular and liquid component of whole blood for specific treatment of specific deficiencies. The use of platelets, plasma protein fraction, serum albumin, fibrinogen, cryoprecipitate, and other antihemophilic concentrates has become routine in all medical centers and common in smaller institutions.

Correspondingly, the procurement of blood has become more difficult as the need for transfusion continues to rise. On this logistic basis alone, many have called for the

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specific use of packed red cells instead of "shotgun therapy" with whole blood.^{1,3-5,10,11,14} The advantages of packed cells are as follows: 1.) diminish likelihood of congestive heart failure;⁷ 2.) less infused ammonia, potassium, and other acid products; 3.) fewer allergenic proteins; 4.) possible reduction in hepatitis;^{1,14,15} 5.) decrease chance of isosensitization which could complicate future pregnancies and/or transplantation;³ 6.) greater safety when nonspecific blood is required;¹⁰ 7.) fewer donors will be required; 8.) non-required components can be used in other patients.¹⁶

A rational approach to the use of blood products should be based on factual clinical evidence where possible and not on empirical findings alone. Heretofore, preference for component therapy in elective operations has been based on empirical findings. Schorr and Marx transfused the first two units of blood in elective procedures as packed red cells plus 250 ml lactated Ringer's solution; the blood transfused after the initial two units was half packed red cells and half whole blood. They found blood pressure and urine output to be well maintained and saw no evidence of increased intraoperative or postoperative morbidity or mortality. The authors recognized these observations as empiric and uncontrolled.¹⁰

The goal of our study was to evaluate objectively the effects of primary use of packed cells or whole blood for transfusions in elective operations. We sought scientific and/or statistical evidence to support or refute the contention that specific component therapy is to be preferred. This study may also serve to define factors essential to ultimate comparative evaluation of the use of frozen cells in elective surgical situations.

Presented at the Annual Meeting of the Southern Surgical Association, December 9-11, 1974, Boca Raton, Florida.

Supported in part by a grant from Red Cross Regional Blood Bank, Louisville, Kentucky.

TABLE 1. Comparison of Treatment Groups

	Patients Allocated Whole Blood	Patients Allocated Packed Cells
1. Number of patients	155	139
2. Previously transfused	39	32*
3. Reaction to prior transfusion	1	1
4. Males	45	44
5. Females	110	94
6. Females with questionable pregnancy	3	1
7. Mean number pregnancies/ woman	4.3	3.7
8. Rh factor abnormality	4	1
9. History of autoimmune illness	1	1
10. History of allergy	20	17
11. Mean patient age	45 yrs	43 yrs
Range	(14-87)	(12-88)

*An additional patient was suspected to have been transfused.

Materials and Methods

The study group involved all elective general, thoracic, and gynecologic operations, excluding only cardiopulmonary bypass procedures. The study group was randomized into two groups according to the last number in the patient's hospital number. If the last number was even, the first three units the patient received were packed red cells; if the last number was odd, the first three units received were whole blood. Units of blood in excess of those customarily prepared for a given procedure were not set up for the packed cell group, and plasma products were not given in conjunction with the packed red cells. The "whole blood" and "packed cells" groups had subgroups

TABLE 2. Use of Prepared Blood

Patients Allocated	Prepared	Used
Whole Blood	370	63
Packed Red Cells	326	44
Totals	696	107

of transfused patients and patients not transfused. The latter patients acted as within-group controls.

The red cells were "packed" by centrifugation followed by mechanical squeezing to separate plasma and red blood cells. This was done at the Red Cross Regional Blood Center with subsequent transfer to Louisville General Hospital.

A data card was compiled for each patient, including the specific estimated degree of surgical trauma, estimated blood loss according to both the anesthesiologist and the surgeon, number of units of blood prepared and actually used, age of used blood, any transfusion reactions to other blood products used, complications, and length of postoperative hospital stay. Laboratory data included preoperative laboratory values for hemoglobin, hematocrit, potassium, albumin, calcium, bilirubin, and clotting factors. Early (within 48 hours) postoperative and late (more than one week) postoperative laboratory values as above were also determined as clinically required for satisfactory patient care.

Levels of 2, 3—diphosphoglyceric acid, in patients requiring greater than 4 units of blood intraoperatively, were determined colorimetrically immediately after operation in the recovery room and repeated 24 hours later.

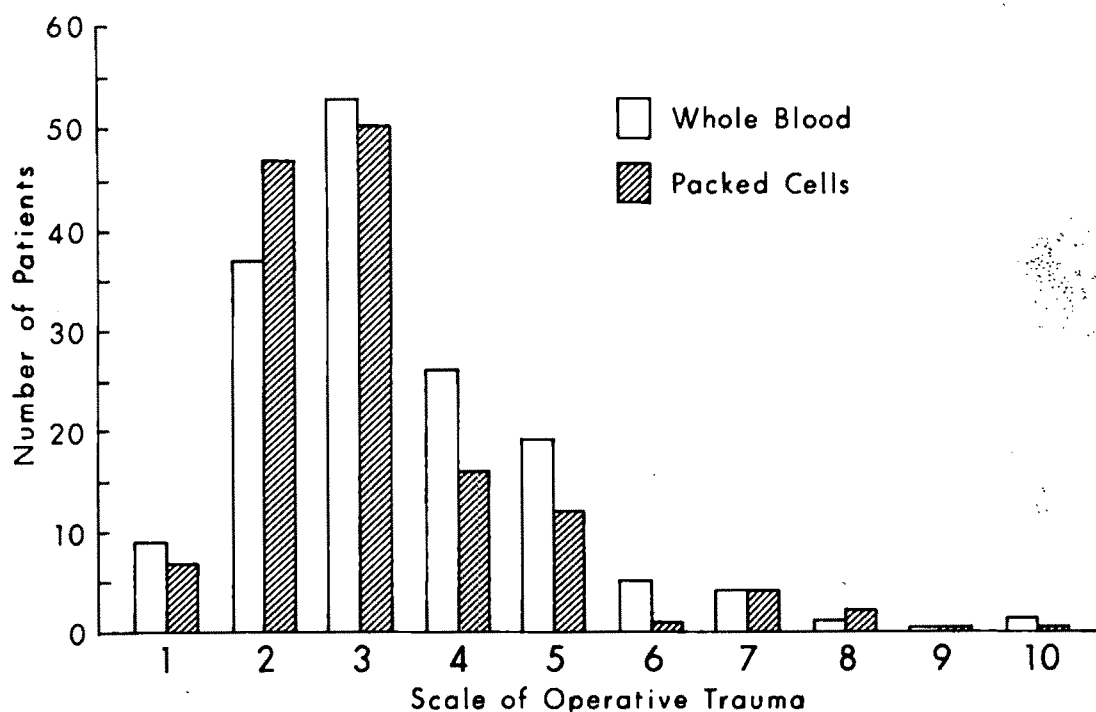


FIG. 1. Comparisons of the magnitude of operative trauma according to the scale introduced by Moore⁶ show a similar distribution between the study groups.

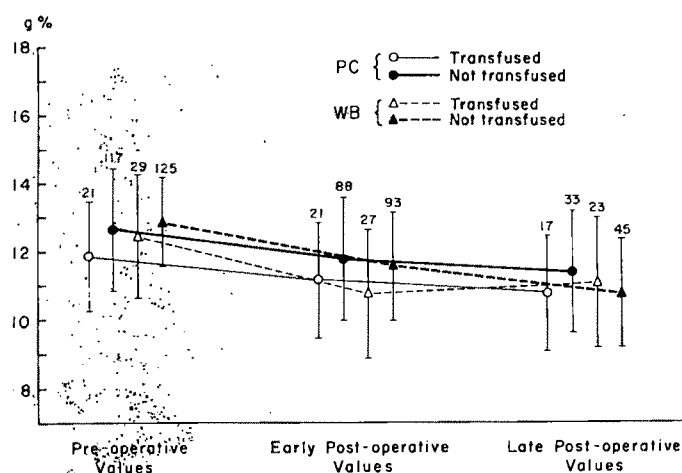


FIG. 2. Changes with respect to time in hemoglobin concentration are similar for all groups. Analysis of variance (Linquist Type III) shows no difference between groups but similar difference across time within a group for all groups. Brackets indicate $\pm$ one standard deviation and the superscript numerals reflect the number of observations from which the mean is calculated.

Results

During the 4 months of this survey, a total of 294 patients were allocated between a whole blood and group totaling 155 and a packed cell group numbering 139. These two groups were similar in all respect (Table 1) and appear to provide adequate populations for an unbiased comparison.

The severity of the operative procedures carried out were similar (Fig. 1). Most patients had procedures scaled 2-5 in both the packed cell group and the whole blood group.

In this university teaching hospital, the number of units of blood prepared for use in elective operations as opposed to the number of units actually used was 6:1; a total

TABLE 3. The Frequency of Complications According to Transfusion Status

	Complications	
	Present	Absent
Whole Blood Group		
Transfused whole blood only	6	8
Transfused whole blood and other blood products	10	3
	(16)	(11)
Transfused other blood products only	10	4
Not transfused	28	86
Group Totals	54	101
Packed Cells Group		
Transfused packed cells only	7	5
Transfused packed cells and other blood products	5	6
	(12)	(11)
Transfused other blood products only	7	10
Not transfused	23	76
Group Totals	42	97

TABLE 4. Use of Blood Products Relative to Operation*

	Before	During	After	Total
Whole blood	11	4 + 29	17	61
Packed cells	17	0 + 22	16	55

*28 patients in each group received other blood products.

of 696 units of blood were prepared and 107 units of blood were transfused (Table 2).

Serial laboratory determinations of hemoglobin, potassium, albumin, calcium, and bilirubin concentrations during the preoperative, early postoperative, and late postoperative periods are shown in Figs. 2-6.

The age of the packed cells (8.8 days) was significantly greater than the age of whole blood (10.9 days) used in this study ($P < 0.05$).

The whole blood group receiving blood had a mean blood loss of 1054 ml according to the surgeon and 1240 ml according to the anesthesiologist. The packed cell group receiving blood did so after losing a mean of 991 ml (surgeon's estimate) and 885 ml (anesthesiologist's estimate). There is no difference in the groups as judged by the surgeons' estimates. The difference with respect to the anesthesiologists' estimates may be significant because anesthesiologists usually initiate transfusion in this operating suite; it may be that they were likely to begin transfusion sooner (i.e., with less blood loss) in patients known to have been allocated to the packed red cell group.

Two febrile blood transfusion reactions were noted, one for each group.

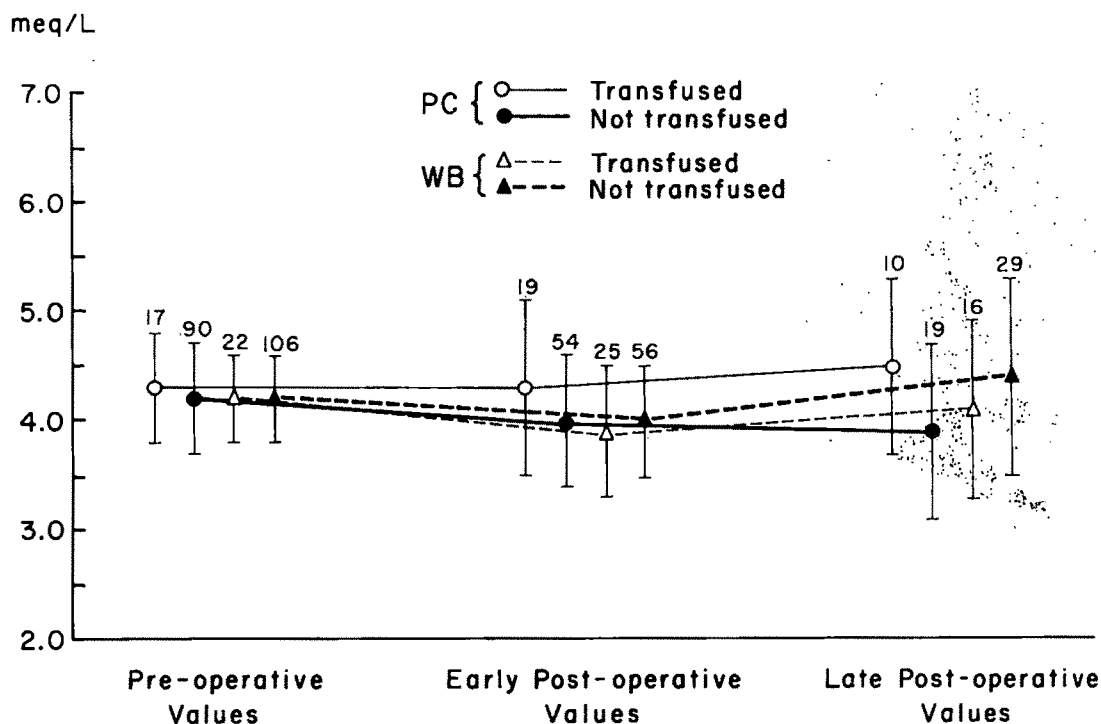
Two patients received more than 4 units of blood. Determination of 2, 3-diphosphoglyceric acid levels immediately postoperatively and repeated determinations 24 hours after transfusion were found to be within normal limits in each instance.

Twenty-eight patients in the whole blood group as well as 28 patients in the packed cell group were given blood products other than that prepared as survey blood. Only 4 units of non-randomized blood products were used for intraoperative transfusions (Table 4).

The duration of postoperative hospitalization was longer among transfused patients than among those not requiring transfusion. No significant differences in the length of stay was found between those receiving whole blood and those receiving packed cells (Fig. 7).

The requirement for transfusion obviously presages a variety of secondary results. First, patients transfused with whole blood or packed red cells had a higher frequency of complications than patients not transfused but allocated to similar groups. The complication frequency appeared to be independent of the kind of blood used. Whether whole blood or packed cells, the frequency of complications increased in number among patients requir-

FIG. 3. Changes with respect to time in potassium concentration do not occur between or within the four groups.



ing transfusion. The combined complications of patients receiving whole blood or packed cells and/or other blood products are summarized in Table 3.

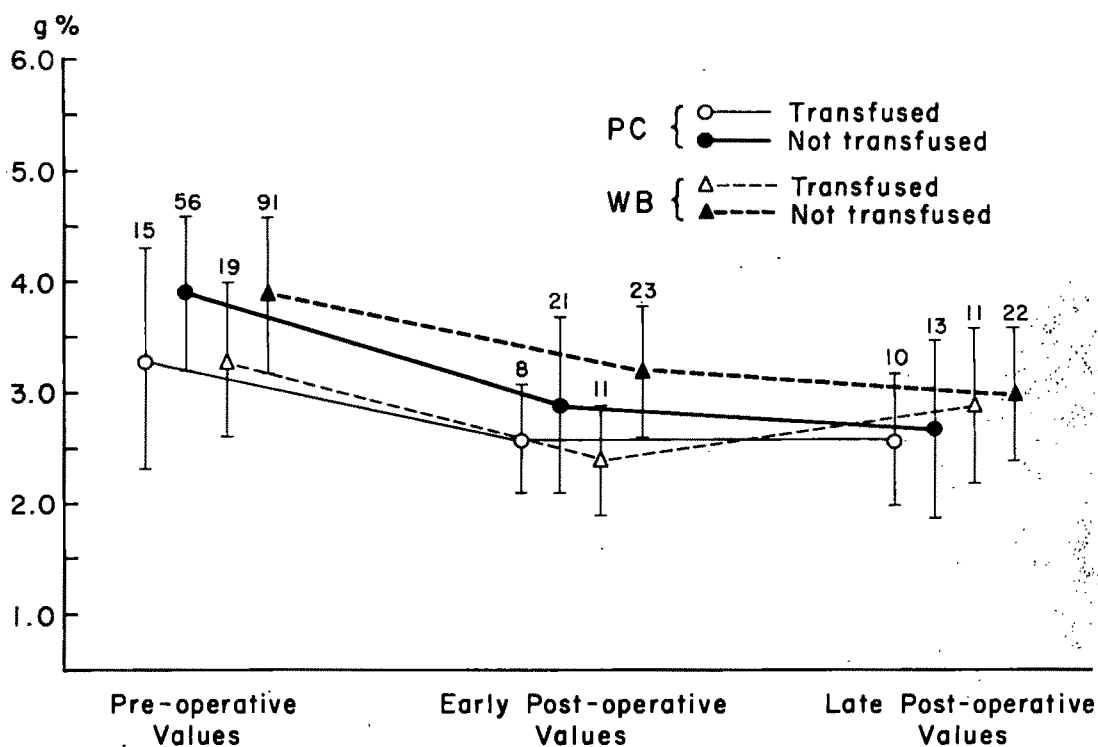
Five of the 155 patients randomized to the whole blood group and 8 of the 139 patients allocated to packed red cells died in hospitals. None of the deaths were clinically correlated with transfusion or related factors. No differ-

ence was found in laboratory determinations of clotting factors in either group. No clinical bleeding diatheses were detected.

Discussion

There are two related, primary hazards of blood loss: inability to maintain adequate blood pressure and, there-

FIG. 4. Changes in albumin concentration are displayed, but there were too few patients with data at all three periods to allow meaningful tests of significance.



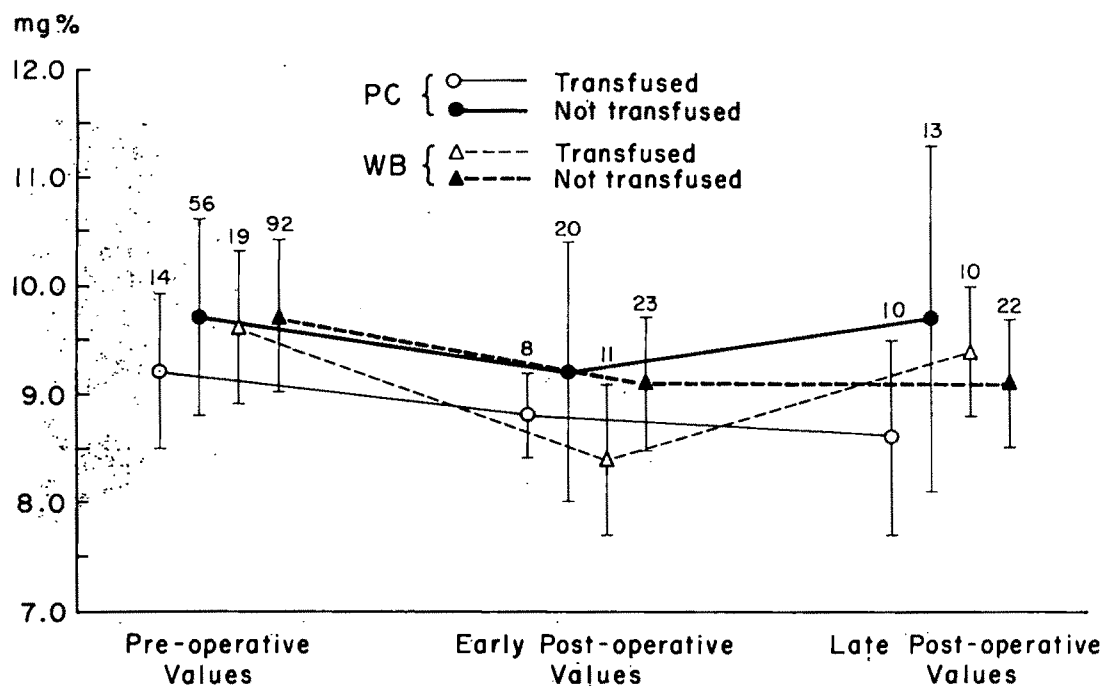


FIG. 5. Changes in calcium concentration are depicted; there were too few patients with data at all three periods to allow meaningful tests of significance.

fore, inadequate oxygenation of vital tissues. Schorr and Marx have reported blood pressure and urine output to be well maintained when using packed cells in elective operations.¹⁰ This study indicates that the level of hemoglobin is not significantly altered postoperatively by use of either whole blood or packed cells for transfusion. By implication, either method provided the essentials of oxygenation both immediately and subsequently. Subjective examination of the anesthesiology records of the patients surveyed shows that there was no difficulty in maintaining blood pressure in either group.

Postoperative albumin concentrations disclosed no difference between the groups despite the inclusion of

plasma in the whole blood group and its exclusion from the packed red cell group. Indeed, patients needing transfusions to increase the hemoglobin concentration do not need transfusion to maintain albumin levels. Because the amount of albumin does not significantly change, there should be no difficulty in volume maintenance, protection from infection, or promptness of wound healing. Thus, measurable abnormalities do not ensue if albumin loss via hemorrhage of the magnitude in these patients is not replaced.

Our data strongly indicate that patients requiring blood transfusion have an increased frequency of complications, irrespective of the nature of the transfused fluid. Similarity in complication rates between groups is further evi-

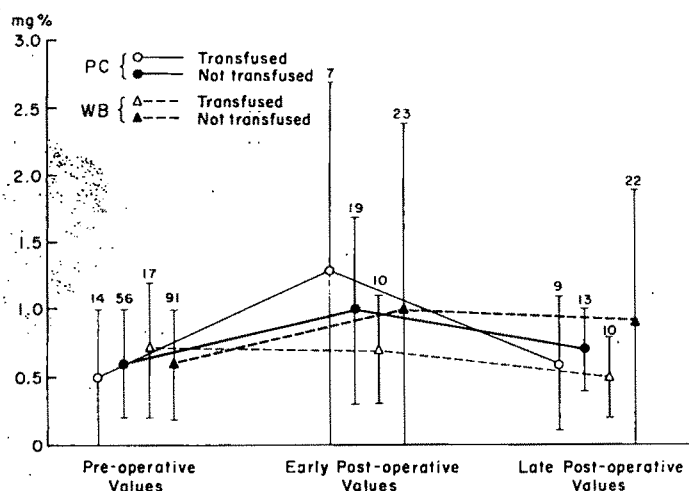


FIG. 6. Changes in total bilirubin concentration reflect the small numbers of patients studied at each period, precluding statistical evaluation. Extreme elevations in the early postoperative period regularly were attributable to hepatobiliary operations.

GROUP	5	10	15	20	25	RANGE (DAYS)
Randomized to Whole Blood Transfused and Untransfused						1-65
Randomized to Packed Cells Transfused and Untransfused						1-177
Whole Blood - Transfused						6-65
Packed Cells - Transfused						5-177

FIG. 7. The duration of postoperative hospitalization among patients surviving operation was similar for those randomized to either group and not transfused and for those transfused, regardless of what blood preparation was employed. The horizontal striped section is that which is added to the mean of the rest of the group when the extreme longest hospitalization is included.

dence that the use of packed red cells bears no delayed hazard.

Indeed, one might well accept the number of complications in such a prospective, similarly distributed study to be the ultimate expression of the effects of specific types of transfusion. Although the frequency of complications is similar within and among the comparable groups (Table 3), there is still a chance that a Type II statistical error has been made; i.e., we have not found a difference between the whole blood and packed cells groups when one really does exist. As a matter of fact, the power of the test is under 50%; to raise this to an acceptable 80% level, maintaining the presently demonstrated rates, would require 72,301 patients receiving whole blood and 54,949 patients receiving packed red blood cells. Even though the only way to exclude a Type II error is to continue the study, the limits necessary to reach an acceptable power of the test are themselves strongly indicative that the two blood products studied are not determinants of the frequency of postoperative complications.

Although the difference in the age of the blood was significantly different, one may suggest that the age of blood (to the extent noted between the groups) is not related to complications among transfused patients or that the adverse effects of old blood is counterbalanced by other benefits of the use of packed cells. The age difference may be insignificant because concentrated red cells stored for 25 days have a 70% survival 24 hours posttransfusion.¹²

The 2-10% incidence of transfusion reactions nationwide is anticipated to decline with the use of packed cells.² No evidence to support the decrease in blood reactions which might be expected in blood with fewer protein fragments—i.e., packed cells—was found in this survey. Indeed, only washed-frozen, packed red cells have almost all leukocytes, platelets, and plasma removed.¹⁵ Centrifuged, packed cells with the buffy coat separated still contain 30% of the original leukocytes, less than 30% of the platelets, and 5-10% of the plasma originally in the whole blood.³ Thus, even though the amount of extraneous protein is decreased, it may not be clinically significant. Logically, the use of subzero, glycerol-washed, packed cells will decrease the incidence of transfusion reactions and the incidence of hepatitis.³

Isoimmunization has become a growing problem in medicine.¹³ Packed cells have not been proved to cause less isoimmunization. Initial studies have shown frozen, thawed, leukocyte-depleted red cells had tritiated thymidine values and ratios comparable to those of a

control group indicating no increase in synthesizing DNA in mononuclear leukocytes.⁹

The number of units of blood set up for use is exceedingly high as compared to the number of units used. This is probably a result of the large number of trainees in a teaching hospital but should remind all surgeons in review their "routines."

That packed cells have proved equally effective as whole blood may encourage and facilitate that most ideal but most cumbersome of transfusion practices—autotransfusion and plasmapheresis.

Acknowledgment

The authors wish to thank Ellis Fuller, M.D., for advice and logistic support and Carl O. Knutson, M.D., and Kay Scott, M.A., for statistical consultation. The assistance and cooperation of the Surgery, Gynecology, and Anesthesiology staff and the operating room nurses and ancillary staff are also acknowledged.

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Letter to the Editor

May, 1974

Dear Editor:

There appears in this issue an article describing forceful dilatation of esophageal strictures accompanied by anti-reflux surgery; promising early results are reported. Our experience with this difficult problem dates back to 1953. Thirty-nine such patients were operated upon by this method during the ensuing ten years. It became apparent that the recurrence rate for both hiatal hernia and stricture was very high, over one-half the patients requiring either prolonged bougienage or further surgical procedures.

Most strictures secondary to reflux peptic esophagitis are superficial, readily dilated, and tend not to recur after successful anti-reflux surgery. Clearly, pliable esophageal mucosa develops when further acid-peptic insult is prevented. This is not true, however, in the tough, fibrous, transmural strictures. The dense, fibrous scar contracts both concentrically and longitudinally, re-

sulting in shortening of the distal esophagus. Pliability in the proximal esophagus permits reduction below the diaphragm, but the repair is done under tension with, inevitably, a high incidence of recurrent hiatal hernia and recurrent reflux.

Forceful fracture of these strictures produces multiple tears in the fibrotic wall. These heal by granulations followed by ingrowth of fibroblasts and maturing, contracting fibrous tissue. In some patients prevention of reflux will lessen the reaction, but the incidence of recurrent stricture is unacceptably high. The patch graft method, described by Thal, et al.,¹ follows the sound surgical principle of advancing normal, pliable well-vascularized tissue to replace the fibrous scar. This procedure, when accompanied by an anti-reflux maneuver, is much more likely to produce an enduring, satisfactory result.

E. R. Woodward, M.D.

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MANAGEMENT OF TRAUMA: Pitfalls and Practice

Covers every aspect of the management of trauma, its medical and surgical management, and the special problems it presents. All aspects of practical hospital management are included, with considerations of clinical features, difficult problems, and potential pitfalls. Presented are physiologic considerations of particular importance in trauma such as metabolic and nutritional considerations, shock and special problems in trauma in the aged, addicted and alcoholic. A section is devoted to management of specific injuries. Provides practical information for those called upon to deal with trauma cases which are constantly presented today in medical facilities. Edited and with contributions by **ALEXANDER J. WALT, M.D.**, and **ROBERT WILSON, M.D.**, both of the Wayne State University, Detroit, Michigan. (43 Contributors). About 625 pp. (7 x 10), 124 illus., Ready Soon, 1975.

INFLAMMATORY BOWEL DISEASE

This book is a long needed, broad-base account of non-specific inflammatory bowel diseases—regional enteritis, jejunoileitis, ileocolitis, Crohn's disease of the large bowel, and ulcerative colitis. The result of decades of in-depth studies, the text features authoritative presentations by physicians and surgeons who are actively involved in dealing with these diseases. It provides clear and concise descriptions and gives definitive approaches to their diagnosis and medical and surgical treatment. Initial chapters cover epidemiology and various etiologic considerations. Following are considerations of clinical features, complications, inflammatory disease during pregnancy and in childhood, pathologic features, and radiology. Edited and with contributions by **JOSEPH B. KIRSNER, M.D., Ph.D.**, University of Chicago, Chicago, Illinois; and **ROY G. SHORTER, M.D.**, The Mayo Clinic, Rochester, Minnesota. (25 Contributors). 465 pp. (7 x 10), 240 illus. (20 in color), 1975, \$35.00.

TREATMENT OF SHOCK: Principles and Practice

This excellent work emphasizes both the basic scientific and clinical aspects of the complex phenomenon of shock. Based on the definition of shock as inadequate microcirculatory perfusion, the book provides a logical, unified approach to its treatment. Clinical priorities begin with treatment of the microcirculatory lesion, followed by support of the vital organs and treatment of the underlying cause. The first twelve chapters, each written by a specialist in a specific aspect of shock, present a rationale and outline for therapy based on laboratory and clinical research. The final chapter is a step-by-step outline for therapy. Edited by **WILLIAM SCHUMER, M.D.**, and **LLOYD M. NYHUS, M.D.**, both of the University of Illinois College of Medicine, Chicago. (18 Contributors). 208 pp., 30 illus., 1974, \$12.50.

ANATOMY: A Regional Atlas of the Human Body

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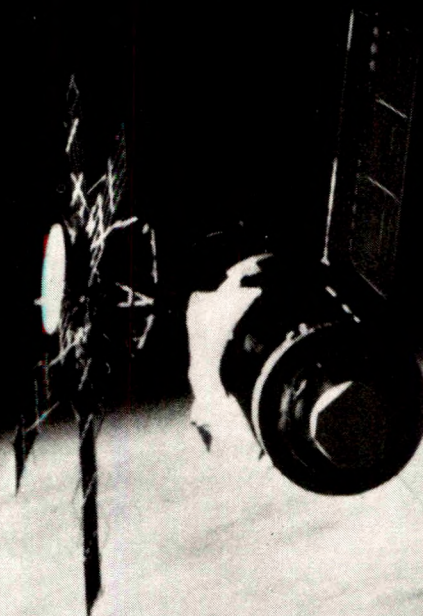


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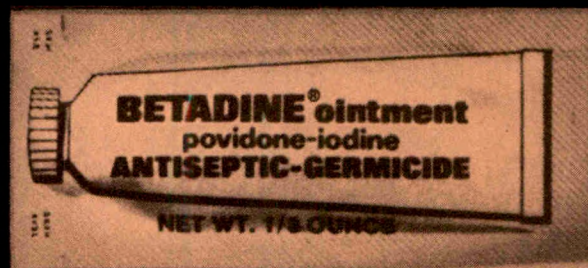
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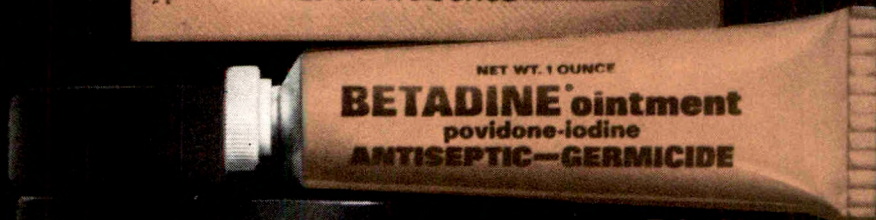
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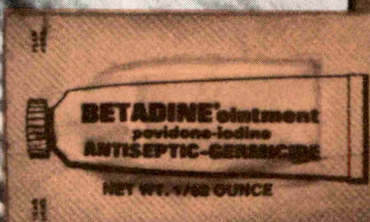


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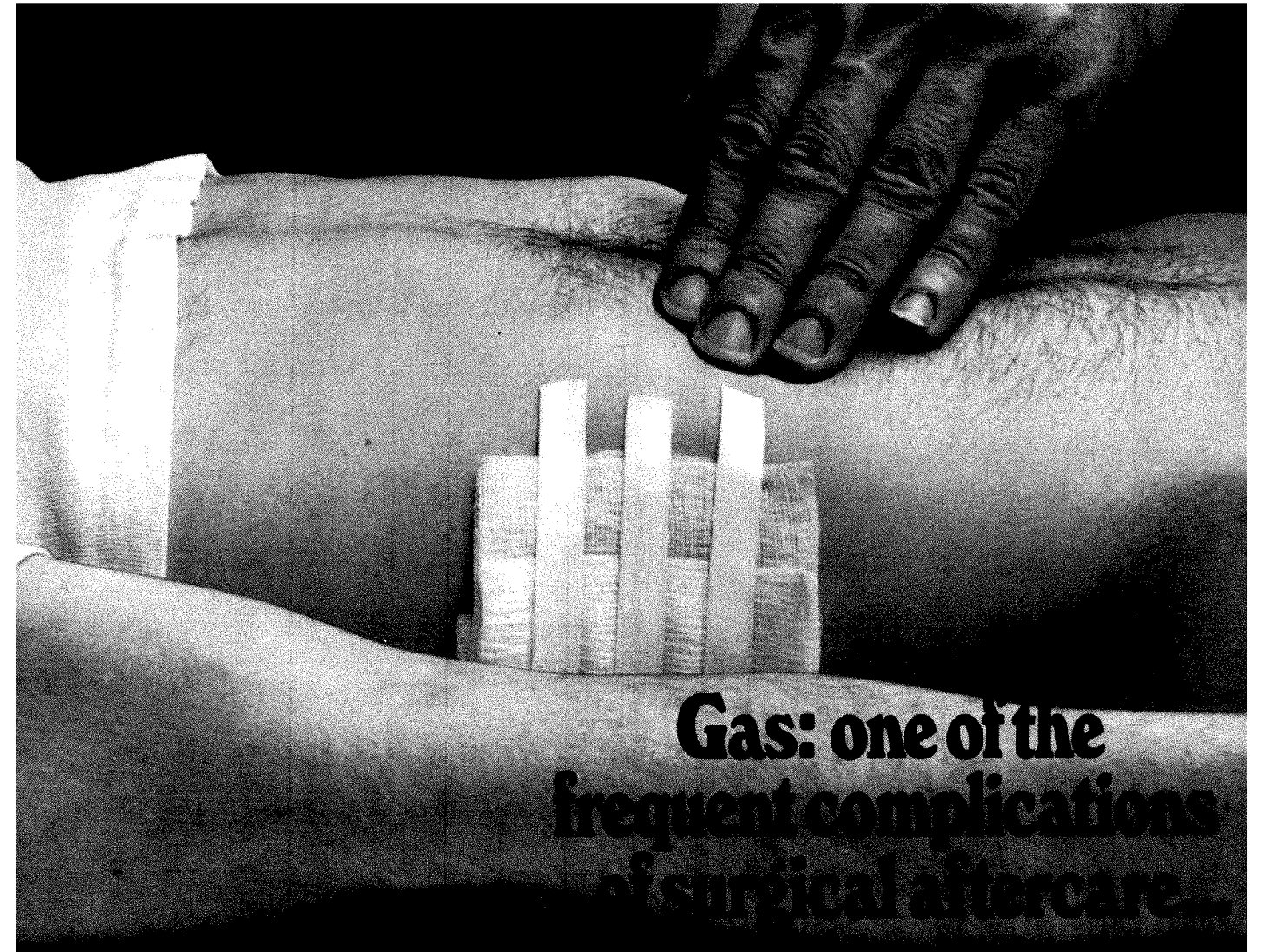
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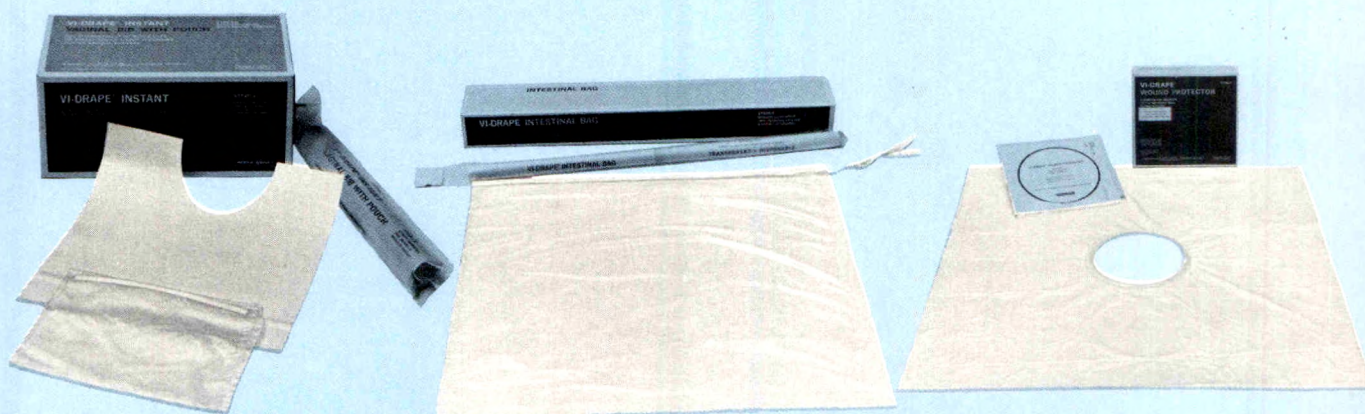
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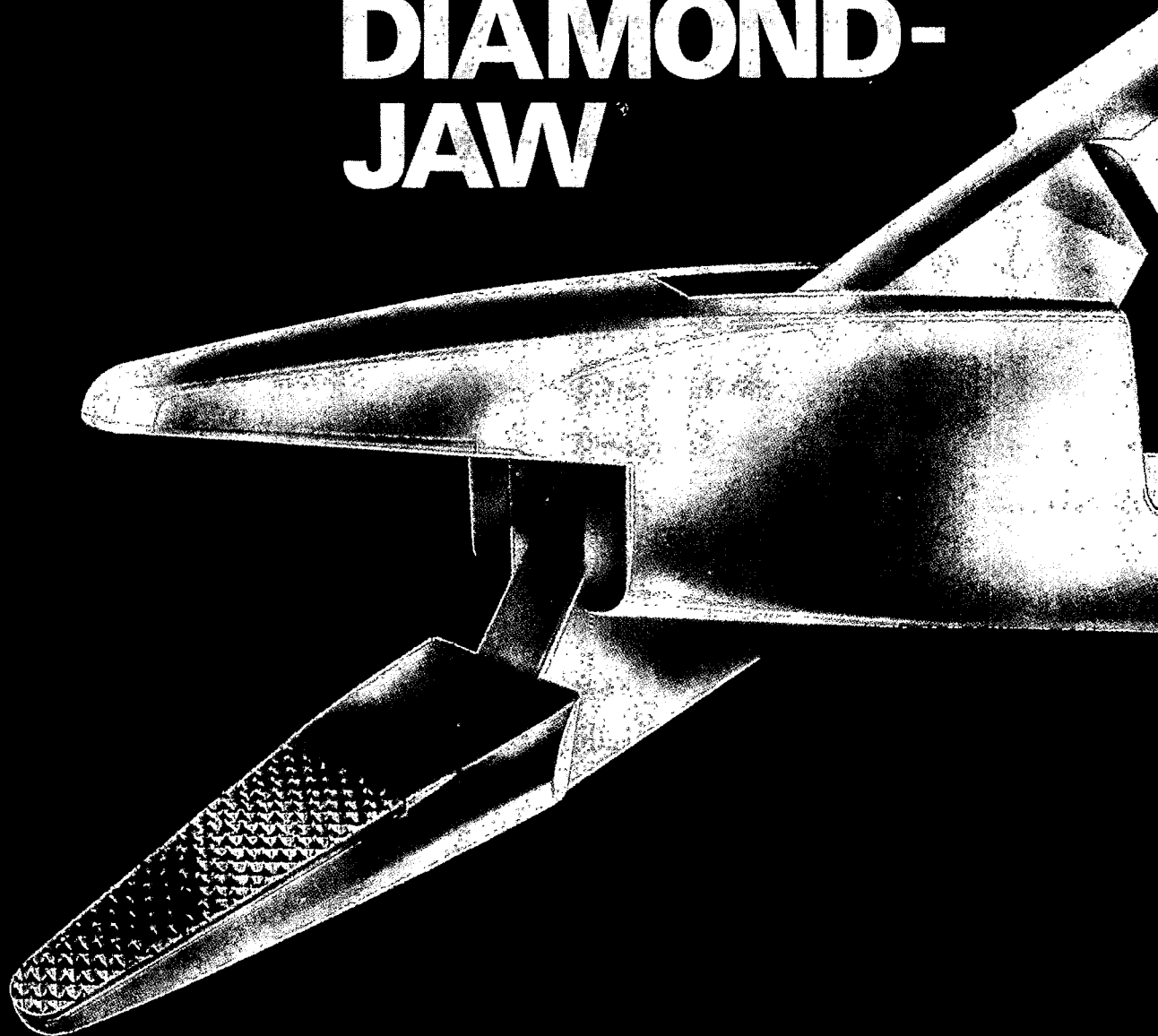
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Editorial:

Wound Irrigation Versus Wound Debridement

THE CAREFUL STUDY by Dr. Hamer and his colleagues in this issue of the Journal adds substantially to an accumulation of data showing that pulsating jet lavage is very effective in removing bacteria and foreign material from surgical wounds. There is danger, however, that some surgeons will misinterpret the findings.

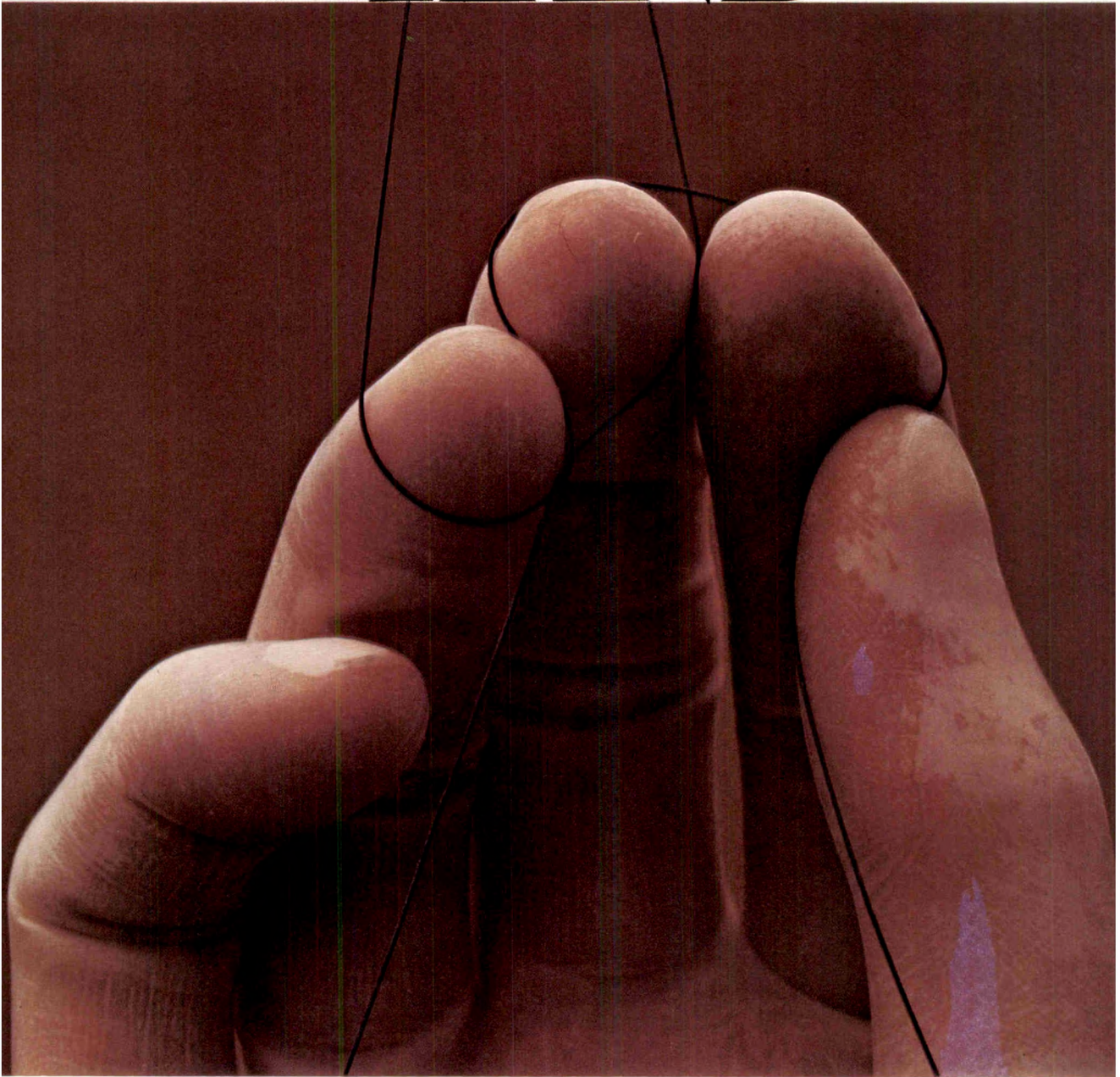
For generations, many surgeons, at the conclusion of an operative procedure, have gently flushed operative wounds with saline. Empirically, it can readily be demonstrated that if vigorous syringing is used, there is a curious blanching and pallor of the subcutaneous layer. Most Halsted-trained surgeons, therefore, have simply gently filled the wound with saline and then aspirated it, removing, thereby, fragments of detritus. As noted by the writers, there is little evidence that this technique reduces the bacterial content of the wound. Nevertheless, in the hands of many distinguished Halstedian surgeons, ideal surgical technique combined with a gentle saline flush has been associated with infection rates of less than one per cent in clean wounds. Unfortunately, other Halstedian surgeons have experienced a similarly low rate of infection on the basis of careful technique alone without using a saline irrigation. Indeed, one of the well known disadvantages of using normal saline is that it is hypertonic to normal cells. Ideally, Gey's solution or similar preparation clearly not injurious to cultured cells should be used.

It should be made clear that the study by Dr. Hamer applies primarily to traumatic contaminated wounds. Pulsating jet lavage in these circumstances is a method of debridement. As his studies show, it not only removes bacteria, but large amounts of foreign tissue. Most surgeons thoroughly experienced in the management of badly traumatized, heavily contaminated wounds have always opted to leave the skin and subcutaneous tissue open. Despite the encouraging results of Dr. Hamer's group in the use of jet lavage in rats, it must not be assumed that this method of debridement will permit primary closure of the heavily contaminated, traumatized wound.

Moreover, in view of the essentially ideal results of simple, careful Halstedian technique in closed wounds, such as herniorrhaphies or thyroidectomies, and despite the fact that it is known that bacteria can be cultured from these wounds at the time of closure, there is no justification for employing jet lavage. Indeed, one can raise the question that the inevitable associated tissue trauma might lead to an increase rather than a further decrease in the very low incidence of suppurative wound infection in the primarily closed clean wound.

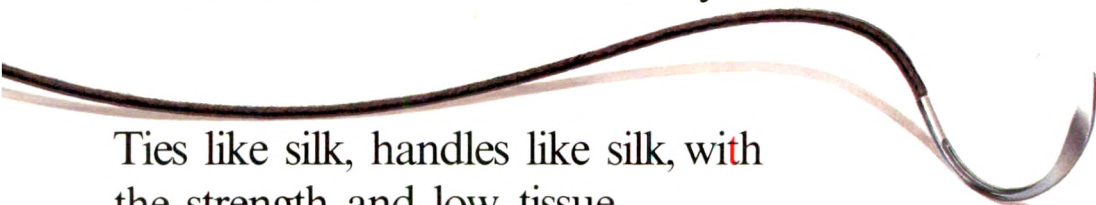
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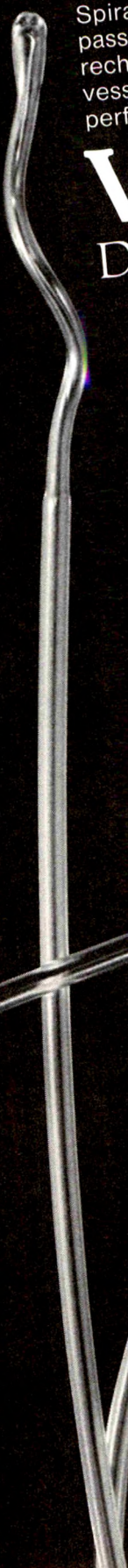


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ANNALS OF SURGERY

Vol. 181

June 1975

No. 6



False Aneurysm as a Late Complication of Anterior Dislocation of the Shoulder

JOSEPH F. FITZGERALD, M.D., F.A.C.S.,* JOHN KEATES, M.D., F.R.C.S.†

A review of the literature since 1947 fails to show a report of a false aneurysm with uncomplicated anterior shoulder dislocation. If this potential late complication is to be diagnosed and treated before the patient is released from followup medical care, careful attention must be given to alterations in the radial pulse prior to reduction. Patients who demonstrate an abnormal radial pulse which reverts to normal following reduction should have an angiogram. Pathological findings to the underlying axillary artery must be repaired promptly. Anterior dislocations of the shoulder account for approximately 50% of all dislocations and tend to be most frequent in healthy males. Late vascular complications associated with this injury are infrequent and can therefore be easily overlooked as illustrated in this report.

A 57-YEAR-OLD Caucasian woman was mugged while getting off the subway in New York City. One of her assailants struck a heavy blow to her left shoulder during the course of the attack. The patient was taken to the Emergency Department of the Kings County Hospital Center, where a clinical diagnosis of anterior shoulder dislocation was made on the basis of an empty glenoid fossa, and the subcoracoid position of the humeral head. In addition pulses were absent at her left wrist. X-ray confirmed the subcoracoid dislocation of her left shoulder, which was reduced under Demerol analgesia. Following reduction her left radial pulse returned to normal. Angiography was carried out and demonstrated damage to the intima of the axillary artery (Fig. 1); nothing was done at this time because the patient was asymptomatic and had normal pulses. It was felt that this intimal injury would heal and cause no further difficulty. The patient

From the Downstate Medical Center, Department of Surgery, 450 Clarkson Avenue, Brooklyn, New York

made an uneventful recovery, and after an appropriate interval was discharged from followup care.

Six months following discharge, the patient noted a lump in her left axilla which was progressively enlarging. When the mass interfered with motion at the joint she consulted her own physician, who, finding a pulsatile mass, referred her to Downstate Medical Center for further study and treatment. Physical examination of her left axilla revealed a 7 cm warm expansile mass with an audible bruit, and normal pulses at the left wrist. Angiography showed a large false aneurysm of the axillary artery at the take off of the subscapular artery (Fig. 2).

After additional preoperative evaluation, exploration was carried out through a deltopectoral approach with the arm in full abduction. Proximal and distal control of the axillary artery was obtained prior to exposing the aneurysm. Once arterial control was obtained and the major cords of the brachial plexus isolated, the aneurysm was unroofed and the artery divided between clamps. The damaged portion of the artery was resected and the aneurysmal cavity drained. Vascular continuity was re-established by direct end-to-end anastomosis of the axillary artery. Following surgery the patient made an uneventful recovery and was discharged on the seventh postoperative day. She has remained well and has shown no further evidence of vascular impairment.

Submitted for publication October 7, 1974.

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Reprint requests to: Dr. Joseph F. Fitzgerald, Department of Surgery, Box #40, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203.

Comment

Complications and associated injuries are not uncommon with anterior shoulder dislocation. Most involve the osseous structure such as, 1) fracture; 2) recurrent dislocation; or 3) osteoarthritis secondary to damage at the

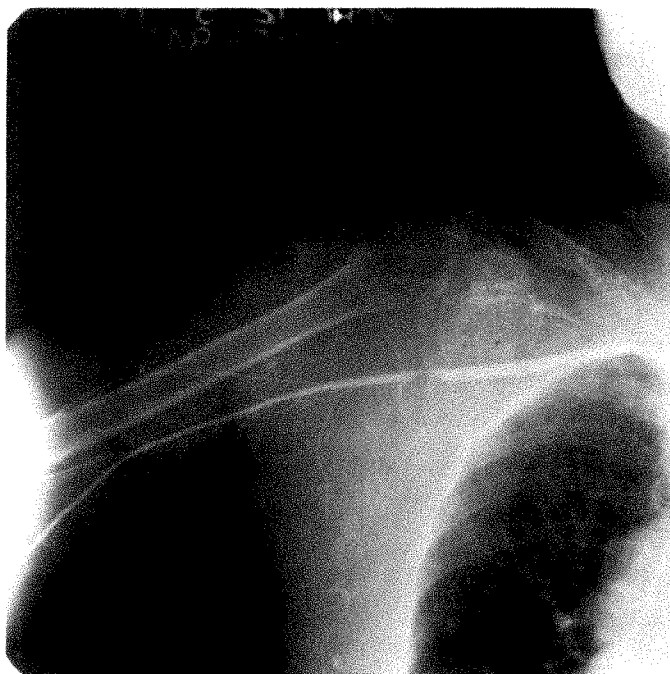


FIG. 1. Immediate post reduction angiogram showing extensive intimal damage to the third portion of the axillary artery with a normal radial pulse.

joint surfaces. Nerve injury, especially brachial plexus palsy, is also encountered. Fortunately, vascular complications are rare and may be conveniently divided into symptoms and signs exhibited early or late.

Early injuries which include traumatic rupture or thrombosis of the underlying axillary artery, are diagnosed and treated promptly because vascular symptoms and signs such as absent pulse, painful cool extremity or massive swelling secondary to hematoma are readily apparent. Late complications, typified by the false aneurysm presented here, may be missed because early symptoms and signs are often minimal and transitory. Alteration in the radial pulse prior to reduction is the most frequent sign of this late vascular complication; usually the pulse is absent or appears and disappears. In addition if a comparison of the blood pressure by palpation of the radial pulses is carried out, it will show diminished pressure and flow in the involved upper extremity. Following reduction these signs revert to normal. With the return of a normal pulse, a physician not experienced with late vascular complications of this injury tends to assume that the alteration of the radial pulse was caused by mere compression of the axillary artery from the dislocated humeral head, and that following reduction with the compression removed the vessel is now functioning normally. Consequently further studies on the vascular system are not carried out, the patient then is treated in the routine manner for this injury, eventually being discharged from medical care.

Therefore if this complication is to be avoided, the potential problem must be diagnosed and treated as soon as possible, preferably before an aneurysm has formed. Patients who, prior to reduction, are noted to have an absent pulse, a pulse which comes and goes or one which is not of normal volume must have an angiogram following reduction. This is especially true of those patients whose pulse has returned to normal following reduction. It is precisely this type of patient who is likely to develop late vascular problems. If angiography shows extravasation or damage to the intima repair must be done as soon as the patient's general condition allows operation, since it can not be assumed that the vessel will heal spontaneously. This was clearly demonstrated in the case discussed above. A false aneurysm once diagnosed demands early surgical intervention. If left untreated it often will rupture with massive if not fatal hemorrhage. Early surgery also is technically easier to carry out, and has a lower incidence of damage to the adjacent brachial plexus and axillary vein.

Conclusions

Anterior dislocation accounts for 50% of all dislocations in man; vascular complications are rare but can occur following this injury.

Early vascular injury presents no problem in management because major symptoms and signs are present. However, late complications can be overlooked due to the paucity of early signs.

The most constant finding with this complication is an alteration of the pulse at the wrist prior to reduction, which reverts to normal following reduction. Patients who have an altered radial pulse must have an angiogram prior to discharge. Early operative repair of a damaged artery is indicated.



FIG. 2. Angiogram 6 months following reduction, demonstrating a large false aneurysm of the axillary artery at the take off of the subscapular artery. The patient had a normal radial pulse at this time.

Sexual Function After Aorto-Iliac Surgery

MARK H. WEINSTEIN, M.D., HERBERT I. MACHLEDER, M.D.

Patients undergoing aorto-iliac operations frequently suffer severe physical and psychological problems as a consequence of postoperative sexual disability. In an attempt to reduce this symptom complex, careful preoperative and postoperative evaluations were performed on 20 patients undergoing such procedures. Their average age was 64 years. Patients were divided into groups distinguished by type of operative procedure and extent of sexual function, then carefully evaluated for changes related to technical aspects of the vascular reconstruction. Data were accumulated pertaining to preoperative and postoperative frequency of sexual intercourse, ability to achieve and maintain an erection, occurrence of retrograde ejaculation, and other symptoms of genitourinary dysfunction. Significant and disabling sexual dysfunction, found to occur after routine abdominal aneurysmectomy, aorto-femoral bypass grafting, and aorto-iliac endarterectomy, is believed to be related to type of operation and technical aspects of the procedure. The incidence of postoperative retrograde ejaculation and impotence was significant.

SINCE LERICHE AND MOREL⁴ first described the "syndrome of the thrombotic obliteration of the aortic bifurcation" in 1948, surgeons have been aware that sexual dysfunction results from atherosclerotic occlusive disease of the distal aorta. With dramatic advances in vascular surgery and greater assurance of good results, as manifest by consistent reduction in morbidity and mortality, vascular procedures are being performed on the abdominal aorta in both young and old patients in increasing numbers. However, relatively little attention has been directed toward the high incidence of impotence and retrograde ejaculation that occurs postoperatively. In view of the decreasing mortality rates for abdominal aortic surgery and the increasing number of elective procedures performed on younger patients, it would seem appropriate to attempt to prevent the severe physical and psychological problems that often are a consequence of postoperative impotence.

Harris and Jepson¹ reported on a group of patients who underwent surgery for Leriche syndrome. Of 6 patients

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who were potent before operation, two complained of postoperative impotence. May *et al.*,⁵ in 1969, reported a 21% incidence of impotence post-aneurysmectomy and a 34% incidence of impotence post-revascularization for occlusive disease. Postoperative abnormalities of ejaculation occurred in 63% of patients undergoing aneurysmectomy and 49% of those undergoing procedures for aorto-iliac obstruction. Sabri and Cotton⁶ interviewed 9 patients under the age of 55. Prior to operation, two were impotent, and seven were potent. After operation 7 were impotent, one was potent, and one had his potency impaired. The present study was designed to assess the incidence of sexual dysfunction after aorto-iliac operation and to relate this dysfunction to the type of operation performed and technical aspects of the procedure.

Materials and Methods

Selected for review were hospital records of 25 consecutive patients ranging in age from 53 to 88 years who had undergone abdominal aortic operations. Their average age was 64 years. Followup examinations were complete for 20 patients who were carefully questioned as to preoperative and postoperative ability to achieve and maintain erection, retrograde ejaculation, frequency of sexual intercourse, and urinary tract symptoms. Operative records were reviewed as to levels and extent of dissection, levels of vascular control, type of operation performed, use of an indwelling urethral catheter, and performance of lumbar sympathectomy. The patients were then classified into three groups, those undergoing aorto-iliac endarterectomy (three patients), aorto-femoral bypass (five patients), and aneurysmectomy (12 patients); their average ages were 57 years, 64 years, and 68 years, respectively. No patient complained of any urinary tract symptoms preoperatively or postoperative-

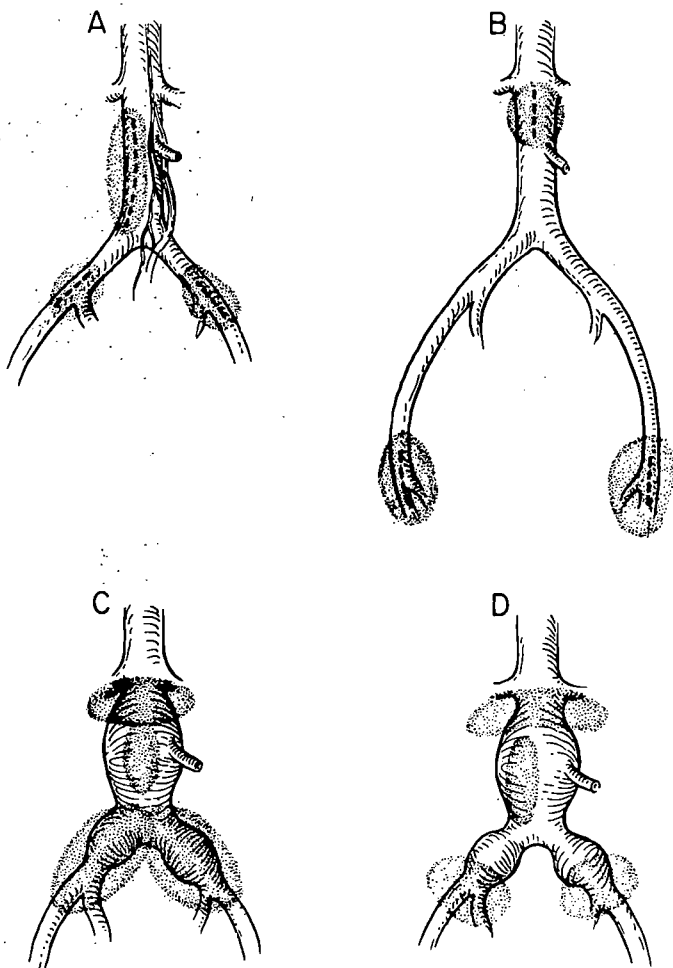


FIG. 1. Areas of dissection for vascular control used in 25 patients undergoing operation on the abdominal aorta: A) aorto-iliac endarterectomy; B) aorto-femoral graft; C) aorto-iliac aneurysm with distal control at common iliac arteries; D) aorto-iliac aneurysm with distal control at external iliac and hypogastric arteries.

ly, and all had indwelling urethral catheters at operation. No patient underwent lumbar sympathectomy, either previously, or at the time of the definitive vascular procedure. Thus, conclusions could be drawn based on the technical aspects of reconstruction without the factor of deliberate sympathetic interruption to consider, and the type of operation could be correlated with sexual dysfunction.

Results

Of the 20 patients for whom follow-up evaluation was completed, 6 patients complained of retrograde ejaculation (30%). Two patients who were potent preoperatively, complained of postoperative impotence (10% incidence).

Of the three patients undergoing aorto-iliac endarterectomy, one was asymptomatic preoperatively and postoperatively, one was impotent preoperatively and postoperatively, and one was impotent preoperatively and

regained his potency postoperatively. No patient in this group complained of retrograde ejaculation. The typical dissection is illustrated in Fig. 1A.

Of the 5 patients who underwent aorto-femoral bypass grafting, 2 were impotent preoperatively and postoperatively, one patient who was potent preoperatively complained of impotence postoperatively, and 2 were unchanged. No patient in this group complained of retrograde ejaculation. Thus, the incidence of impotence in this group attributable to operation was 20% (1 of 5). Area of dissection is illustrated in Fig. 1B.

Of the 12 patients who underwent abdominal aneurysmectomy, none was impotent preoperatively. One patient who was potent preoperatively complained of impotence postoperatively, an incidence of 8%. Six patients in this group complained of postoperative retrograde ejaculation without impotence (50%). The areas of dissection for control are illustrated in Figs. 1C and D.

The level of dissection at the time of operation was examined in the 6 patients who lost ejaculation but maintained potency after undergoing abdominal aortic aneurysmectomy. In 5, the dissection was carried down to the common iliac vessels, and in one, it was carried down to the common femoral vessels. Five of these patients had tube grafts, and one had a Y graft. The back wall of the aneurysm was left in place in all 6 patients. All had extensive dissection of the anterior wall of the abdominal aorta and common iliac vessels. The critical area of dissection in tube graft placement is illustrated in Figs. 1C and D.

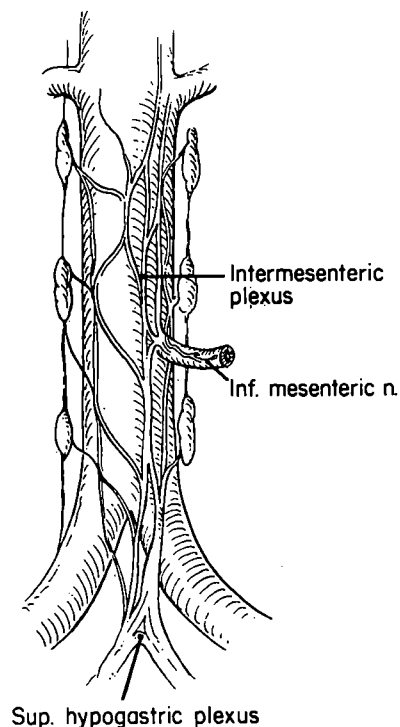
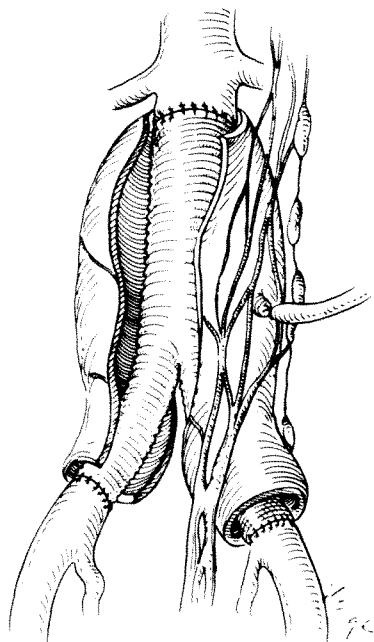


FIG. 2. Normal sympathetic anatomy of distal abdominal aorta.

FIG. 3. Method of aorto-iliac aneurysmectomy preserving sympathetic plexi critical to normal sexual function.



In the two patients who lost their potency as a result of the operation, dissection was carried down to the iliacs in one who underwent aneurysmectomy, and extensive dissection of the hypogastric area was performed in the other who underwent aorto-femoral bypass.

Of all patients who were asymptomatic preoperatively and postoperatively, the average frequency of sexual intercourse per week did not change significantly. Of the 6 patients who complained of postoperative retrograde ejaculation, frequency of sexual intercourse decreased.

Discussion

The sympathetic nervous innervation of the pelvis is intimately involved in maintaining potency and normal ejaculation. As Harris and Jepson¹ pointed out, many patients with Leriche syndrome improved as far as symptoms of claudication are concerned, but the vascular reconstructive procedures offer little for restoration of potency. They suggested that impotence in these patients is the result of disruption of the pelvic nerve plexus at operation. It has been well demonstrated both anatomically and physiologically that the accessory male genitalia are innervated by the lumbar sympathetic chain via the hypogastric or presacral plexus.² Loss of ejaculation has also been a very common sequelae of presacral neurectomy.³ Spiro and Cotton⁷ have suggested that impotence following aortic surgery is "almost certainly due to interruption of the hypogastric sympathetic plexus which is formed in front of the left common iliac vein by branches descending across the bifurcation of the aorta and particularly its left common iliac division. These branches are inseparable from branches which form a plexus around the inferior mesenteric artery." They

stated that if this plexus is preserved, sexual function can be maintained in 90% of cases.

Whitelaw and Smithwick⁸ have shown that impotency can result from dorsal or lumbar sympathectomy. They stated that bilateral excision of L1 ganglia results in impotency. The sympathetics also innervate the accessory male genitalia. Stimulation of the inferior mesenteric ganglion and the hypogastric plexus causes contraction of the vasa deferens and seminal vesicles. Whitelaw and Smithwick, however, stated that after unilateral resection of the L1 ganglion, ejaculation in man is not usually affected. Other authors have stated that when the L1, L2, and L3 ganglia are removed bilaterally, about 50% of patients suffer loss of ejaculation. Thus, investigators appear to believe that high sympathetic denervation, that is, of L1 or L2, results in impotence, whereas lower sympathetic denervation, that is, of L2, L3, presacral plexus, and hypogastric plexus, results in retrograde ejaculation. Leiter and Brendler³ stated that retrograde ejaculation results from resection of the plexus at the aortic bifurcation. In the present series, no patient had undergone lumbar sympathectomy, yet there was a 10% incidence of loss of potency postoperatively. This would suggest that the dissection of sympathetic fibers at levels other than lumbar ganglionic would result in impotency.

Dissection of the sympathetic fibers around the abdominal aorta as high as the level of the inferior mesenteric artery and as low as the bifurcation of the aorta appears to result in either loss of potency or ejaculation. All 6 of the patients in this study who complained of loss of ejaculation underwent abdominal aortic aneurysmectomy, and most of these patients had interposition tube grafts with extensive dissection of the aorta itself and the common iliac arteries but not below this vessel (Fig. 1C). No patient undergoing endarterectomy complained of retrograde ejaculation or was impotent as a result of the operation. The dissection in these patients was usually at lower levels and less extensive. The arteriotomy incision for endarterectomy is usually medial to the inferior mesenteric plexus, and this plexus is not disturbed. The terminal aorta and the left iliac artery are usually not incised, as the endarterectomy is performed in the left common iliac artery over the hypogastric artery on the left side with an internal endarterectomy stripper. The aortic arteriotomy is usually carried into the right common iliac artery to insure that a good endarterectomy occurs at the bifurcation of the aorta. The presacral plexus is not disturbed except to pass an occluding tourniquet to control the occasionally patent middle sacral artery. May *et al.*⁵ also confirmed these findings.

It would appear that both the extent and level of dissection of the sympathetic fibers of the abdominal aorta determine, in part, postoperative abnormalities of sexual function. Several areas are critical to the preservation of normal postoperative sexual function. The normal sym-

pathetic anatomy is depicted in Figure 2. These critical areas should be left undisturbed with minimal modifications of current operative approach to aorto-iliac reconstructive procedures. In aorto-iliac endarterectomy, the aortotomy should be placed on the right anterior wall of the aorta, avoiding extensive dissection and disruption of the inferior mesenteric sympathetic plexus. The sympathetic nerves along the course of the distal aorta to the point where the presacral plexus is formed should be carefully dissected free of the aortotomy. There is no reason to disturb the left common iliac artery as endarterectomy can be performed with an internal stripper from the traditional arteriotomy over the common iliac bifurcation. These technical factors could enhance return of potency and assure the least disturbance of normal potency in the postoperative period. When an end-to-side anastomosis is performed above the level of the inferior mesenteric artery during an aorto-femoral graft procedure, there is minimal chance of interference with normal potency and ejaculation. No problem should result from passage of the graft retroperitoneally and anastomosis at the level of the common femoral bifurcation.

Patients undergoing aorto-femoral bypass are more difficult to evaluate, since many are impotent preoperatively as a consequence of the basic disease process. In abdominal aortic aneurysmectomy, an operation that results in the most dramatic postoperative sexual changes, it is critical to observe several fundamental technical maneuvers. When the aneurysm terminates before the bifurcation of the aorta, such that the bifurcation is preserved and the conditions are appropriate for insertion of a tube graft, the endo-aneurysmorrhaphy technique of

Creech is used. Care should be taken, however, to dissect the sympathetic nerves from the surface of the aorta and to make the aortotomy to the right and lateral to these important nerve fibers. Control of the iliac artery is obtained at the level of the common iliac bifurcation rather than anterior to the sigmoid mesentery at the aortic bifurcation. When the aorta is completely transected at the bifurcation, the nerve bundle encased in its adventitial investing layers should be preserved. Should the aneurysm involve the iliac segments such that a Y graft is necessary, the same method of endo-aneurysmorrhaphy is used, leaving the left aneurysmal common iliac vessel intact and passing the left limb of the aortic bifurcation graft through this tube of preserved left common iliac artery (Fig. 3). Since rarely do any collateral vessels arise from this segment, this maneuver is feasible and serves to protect the left arm of the graft from the overlying ureter as well as to preserve these sympathetic nerves.

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Inherited Antithrombin-III Deficiency Causing Mesenteric Venous Infarction:

A New Clinical Entity

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Primary superior mesenteric venous thrombosis is sometimes preceded by peripheral thrombophlebitis. Inherited antithrombin-III deficiency is a recently recognized autosomal dominant trait, which is characterized by thrombophlebitis and pulmonary embolism. This case report illustrates many features of both entities and strongly suggests a causal relationship. While long-term therapy has yet to be established, prophylactic therapy is recommended when asymptomatic individuals with known antithrombin-III deficiency are at increased risk of thrombosis. The efficacy of heparin alone has been unreliable, whereas Coumadin has been encouraging. Antithrombin-III concentrates are being developed and theoretically should be helpful. Patients with thrombophlebitis or pulmonary embolism should be suspected of having antithrombin-III deficiency. Such individuals also represent one mechanism to explain "primary" mesenteric venous thrombosis.

INHERITED antithrombin-III deficiency is a recently recognized entity which presents clinically with thrombophlebitis and pulmonary embolism.³ Infarction of the superior mesenteric vein is considered primary when no concurrent, predisposing condition exists. In two large series of mesenteric vein infarction, 32 and 45% of these patients had a history—sometimes years earlier—of thrombophlebitis.^{9,10}

This report describes a 43-year-old man who had a segmental infarction of the superior mesenteric vein and

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a history of thrombophlebitis and a pulmonary embolism. Subsequently he became the propositus in a family with inherited antithrombin-III deficiency. We feel he illustrates one mechanism to explain "primary" mesenteric venous thrombosis.

Case Report

A 43-year-old man (#155 091) was seen initially on 1/7/74 with a 4-day history of right lower chest pain which had spread into the right upper abdomen. His CBC was normal, and arrangements were made to confirm the diagnosis of a mild acute cholecystitis. Thirty-six hours later, his abdominal pain worsened markedly and shifted into the lower abdomen.

Past medical history revealed bilateral simple mastectomies for gynecomastia in 1962. In 1967 he was hospitalized for pneumonia, complicated by bilateral deep leg-vein thrombophlebitis and pulmonary emboli. He was treated with heparin for 2 weeks and Coumadin for 2 months. In 1969 he had another episode of thrombophlebitis.

Physical examination revealed a diaphoretic, obese male in obvious severe pain. His abdomen was obese, soft, silent, and mildly tender in both lower quadrants. Rectal examination revealed normal brown feces, and both legs exhibited painless stasis dermatitis. His blood sugar was 175 mg%, hematocrit 54%, and WBC 14,400 with a mild left shift. Abdominal x-rays revealed an almost gasless abdomen.

Intravenous hydration and antibiotics were begun in preparation for emergency exploratory laparotomy.

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The views expressed by the authors do not necessarily reflect those of the U.S. Army.

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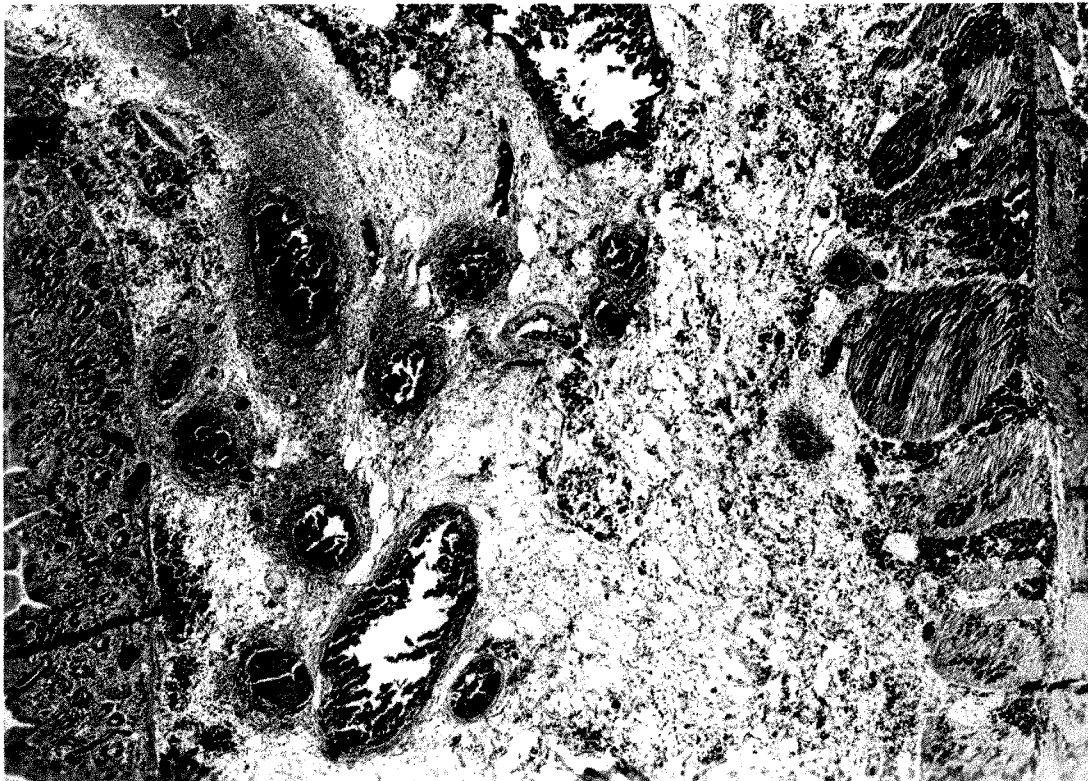


FIG. 1. Hemorrhage and acute inflammation extends through all layers of the small intestine. Severe, acute phlebitis is especially prominent in submucosal veins, and fibrin thrombi are present in mucosal capillaries ($\times 52$).

Operative findings included 1500 cc serosanguinous fluid, a well-demarcated infarction of 85 cm of mid-small intestine, a normal gallbladder, and a diffusely grossly nodular, firm liver compatible with cirrhosis. A 130 cm segmental resection and end-to-end anastomosis of small intestine were carried out.

Thirty-six hours postoperatively his prothrombin time was 14 seconds (control 13 seconds) and partial thromboplastin time was 21.9 seconds (control 31.5 seconds). Intravenous heparin 5,000 μ q4h was initiated. By his 4th postoperative day, he was passing stool and flatus and he was progressed rapidly to a 1500 calorie ADA diet.

Laboratory studies included normal SGOT, bilirubin, alkaline phosphatase, negative LE prep, Bence-Jones protein, antinuclear antigen, cryoglobulins and cryofibrinogen, fibrinogen 300 mg%, platelet count 115,000, IgG 1450 mg% (normal 770-1130), IgA 291 mg% (normal 80-200), IgM 125 mg% (normal 90-170), total serum proteins 8.4 gm% with albumin 48.4% (normal 62-67%), Alpha₁ globulin 3.3% (2.4-4.8% normal), Alpha₂ globulin 15.2% (normal 6.6-13.6%), Beta globulin 13% (9.1-14.7%), and gamma globulin 21.4% (normal 9.0-20.6%).

On his 10th postoperative day, while on heparin and shortly after Coumadin had been initiated, he developed ileofemoral thrombophlebitis of his left leg. This became asymptomatic 5 days later, and he has continued asymptomatic on Coumadin with a prothrombin time which is twice control.

Family History

Antithrombin-III activity of the propositus has ranged from 25% to 31% (normal 85-110%). His daughter (only child) also has antithrombin-III deficiency, while his wife has normal antithrombin-III levels. Currently, plasma from available members of this large family are being examined for antithrombin-III activity. In the absence of consanguinity, an autosomal dominant mode of inheritance is present.

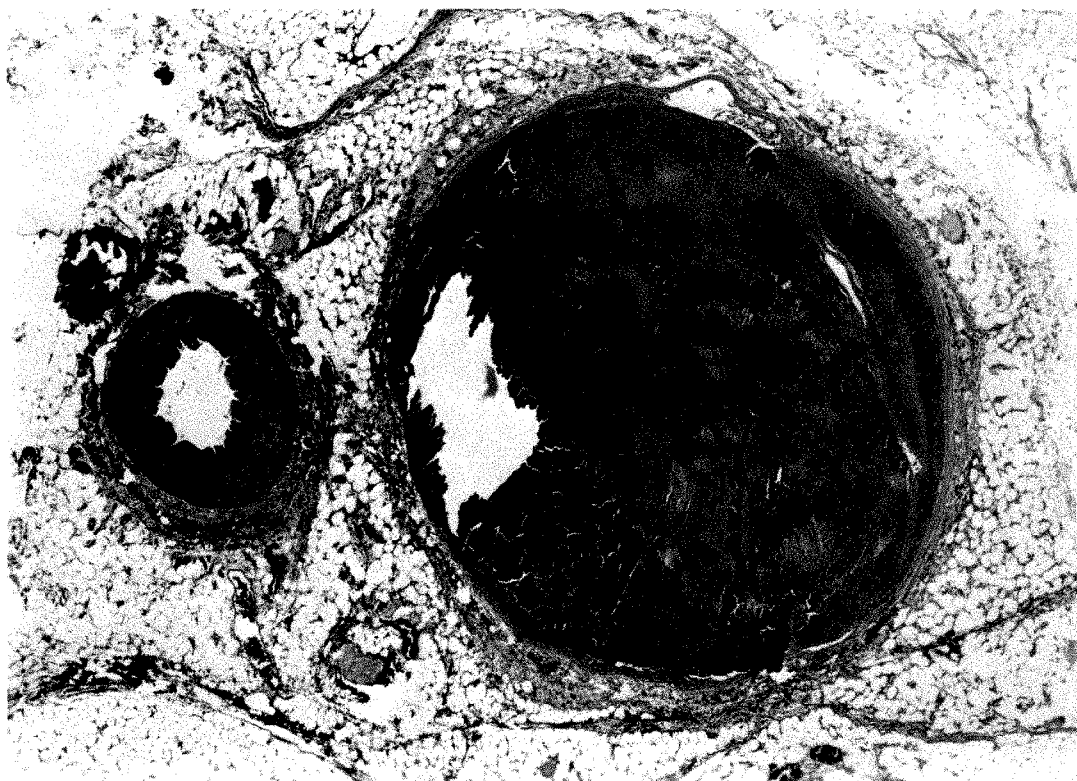
Materials and Methods

Antithrombin-III activity was determined from citrated plasma, using the technique of electroimmunoassay for quantitative analysis of proteins.⁷

Discussion

Since the turn of this century, the activity of thrombin has been known to decrease when exposed to normal serum. This unidentified serum factor was termed "antithrombin."^{12,15} Since then as many as 6 antithrombins have been demonstrated, of which the most important is believed to be antithrombin-III, an alpha-2 globulin of molecular weight 65,000 which is synthesized in the liver.^{12,15} Recently, by electrophoretic and immunoprecipitate biochemical techniques, a 1:1/thrombin: antithrombin-heparin cofactor stoichiometric complex has been demonstrated.¹²

FIG. 2. A large mesenteric vein contains laminations of red cells with fibrin and white cells and exhibits the phlebitic changes present in the previous photomicrograph. The adjacent artery is normal and patent ($\times 18$)



Decreased activity of antithrombin-III has been demonstrated in patients with hepatitis, hepatic cirrhosis, intravascular clotting, shortly after myocardial infarction, venous thrombosis, or pulmonary embolism, and in patients taking estrogen-containing progestational agents.^{1-3,8,15} Increased antithrombin-III activity has been demonstrated in patients with hemophilia, proconvertin deficiency, uremia and congenital or acquired heart disease without hepatic congestion.¹⁵ The significance of the antithrombin-III activity in these situations has yet to be defined.

Of more definite clinical significance is the usual 50% reduction of antithrombin-III activity found in those individuals with inherited antithrombin-III deficiency. Although the usual screening tests for coagulation or fibrinolysis are normal, these people have an increased risk of venous thrombosis of varying severity. These thrombotic episodes generally occur in adulthood and sometimes are associated with conditions having an increased risk of venous thrombosis.^{3,13,14,18}

Invitro testing of plasma and serum of individuals with antithrombin-III deficiency has shown variable resistance to the anticoagulation effect of heparin, and clinical worsening of thrombotic states has been noted on heparin. In view of its variable effect, heparin probably should not be relied upon as the sole agent in treating acute thrombotic or embolic phenomenon. On the other hand, clinical improvement has been noted on oral

prothrombin-depressing agents along with increased or normal levels of anti-thrombin activity.^{1,4,8,15}

While long-term therapy for people with antithrombin-III deficiency has yet to be established, prophylactic therapy definitely should be considered in asymptomatic people with known anti-thrombin deficiency who are in a situation, e.g. elective surgery, post-parturition, where the risk of thrombosis is increased. One possibility is Coumadin employed with care such as not to prolong the prothrombin time beyond twice control. Another possibility is antithrombin concentrates plasmaphoresed from known, high-activity donors. The American National Red Cross currently is developing such a preparation, the half-life of which is yet to be determined.^{16,17}

Earlier reports of mesenteric venous infarction have emphasized the clinical presentation, the significant mortality, the generally segmental intestinal involvement, the importance of wide resection, the tendency of early recurrence, and the importance of postoperative anticoagulation.^{5,9-11} This report illustrates many of these characteristics and demonstrates the autosomal dominant inheritance of antithrombin-III deficiency noted by others.^{3,8,13-15}

Conclusion

People with thrombophlebitis or pulmonary embolism should be suspected of having antithrombin-III deficiency. Such individuals represent one mechanism to explain "primary" mesenteric venous thrombosis.

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Closure of Colostomy

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We analyzed the records of 77 cases of loop colostomy closure in Vietnam War Casualties. All records were complete from the date of injury to discharge following colostomy closure. Simple closure of the loop colostomy was performed in 44 patients and resection of the stoma and reanastomosis of bowel segments was performed in 33 patients. Average operating time for simple closure of the loop was 70 minutes compared to 115 minutes for resection and anastomosis. Nasogastric suction was used less frequently and for a shorter time with simple loop closure. The total postoperative complication rate was 9% with simple loop closure as compared to 24% for resection and anastomosis. Simple closure of the loop described in this report is technically easier and as safe as resection of the stoma and reanastomosis.

THE FIRST COLOSTOMY was successfully performed for trauma in 1795.³ However, it was not until World War II that colostomy became the cornerstone of therapy for injuries to the colon and rectum.^{2-8,15,17,18} While much attention in the literature has been directed towards the indications for colostomy, relatively little can be found on colostomy closure.

Two anatomic and functional types of colostomy have well known and widely accepted indications, i.e. the loop colostomy for exteriorization or decompression, and the double barrel colostomy for complete diversion. Closure of both types of colostomies is generally accomplished by resection of the stoma and end-to-end anastomosis, although some have had success with simple loop closure.^{1,5,7,9,12-14} We also have found that simple closure of the loop colostomy can be done effectively and safely.

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Methods

In a retrospective study, the records of 77 cases of loop colostomy closure performed at Valley Forge General Hospital, Phoenixville, Pennsylvania, Silas B. Hays Army Hospital, Fort Ord, California, and Letterman Army Medical Center, Presidio of San Francisco, California, were reviewed. Colostomies were performed for injuries sustained in combat in Vietnam during the years 1966 to 1971. Cases without complete records from initial injury to closure of the colostomy were not included in the study.

Colostomy closure was not performed until the patient had recovered from his initial injuries and had regained to within 10% of his pre-injury weight. Physical examination, standard laboratory evaluations, sigmoidoscopy, and barium enema were performed in all patients before surgery.

All patients underwent preoperative mechanical bowel preparation for 24 to 72 hours. All but a few patients received both oral and irrigation antibiotics.

Techniques of Closure

In this series the two methods of colostomy closure were 1) simple closure of the loop, and 2) resection of the stoma with anastomosis. Simple closure of the loop colostomy is performed by making an elliptical skin incision around the colostomy and dissecting the bowel from its fascial attachments and intraperitoneal adhesions. A free loop of colon is created so that the closure can be performed outside the abdominal cavity. The stoma edge is trimmed and hemostasis is achieved (Fig. 1a). A Con-

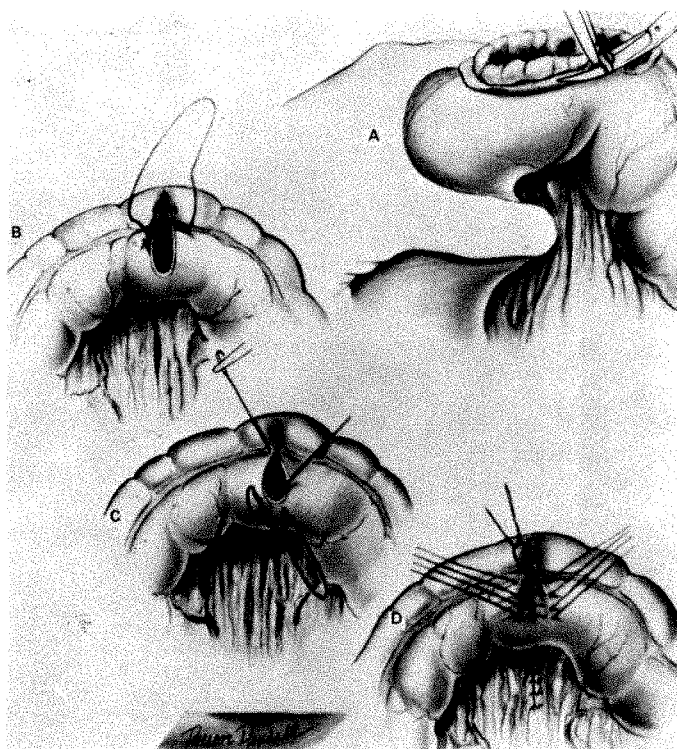


FIG. 1. Simple loop closure. A free loop is created so that closure can be performed outside the abdominal cavity. A, The stomal edge is trimmed. B, A Connell suture is started at both ends with the first stitch placed well behind the corner and tied on the inside. C, Both sutures are brought to midpoint and tied. D, Lembert sutures are placed and the bowel is returned to abdomen.

nell suture is started at both ends with the first stitch placed well behind the corner and tied on the inside. (Fig. 1B). Both sutures are brought to the mid point and tied (Fig. 1C). Lembert seromuscular sutures of 3-0 silk are placed as illustrated (Fig. 1D). The bowel is returned to the abdomen and the fascia is closed. The skin and subcutaneous tissues may be (a) closed primarily, (b) closed over a drain, or (c) closed 4 to 5 days later.

Clinical Data

The average age of the group was 22 years (70% were 21 or younger). Approximately one-third of the injuries

TABLE 1. Associated Abdominal Injuries

Injury	No. Patients	Per cent
Small bowel	26	39
Stomach	14	21
Liver	13	20
Spleen	8	12
Pancreas	2	3
Kidney	2	3
Gallbladder	1	1.5

TABLE 2. Associated Extra-abdominal Injuries

Injury	No. Patients	Per cent
Major fractures	20	33
Chest wounds	14	23
Genito-urinary injuries	9	15
Amputations	6	10
Vascular injuries	4	6
Ophthalmic injuries	4	6
Neck wounds	4	6

were caused by high velocity missiles and two-thirds by relatively low velocity missiles such as Claymore mines, rockets, and grenades. The patients had a variety of associated abdominal injuries (Table 1) and extra-abdominal injuries (Table 2).

In the majority of cases, definitive surgical care was initiated within one hour of injury after helicopter evacuation from the combat site. Severe complications occurred in 63% of the cases wounded by high velocity missiles and in 39% wounded by fragmentation weapons (Table 3). Intraperitoneal abscesses and enteric fistulas occurred frequently. Bowel obstruction requiring lysis of adhesions was also common.

The indications for colostomy are listed in Table 4. There were 77 loop colostomies performed. The average interval from injury to closure was 16 weeks.

Rectal injuries generally were treated with closure of the perforation and proximal colostomy. In Vietnam, Lavenson and Cohen¹⁰ instituted thorough operative rectal washout and noted a significant decrease in mortality. Adequate presacral drainage, with or without coccygectomy, has been established as an important adjunct in the treatment of rectal perforation.^{8,10,11,16} It was not performed consistently in our series until 1970. Loop colostomies with incomplete diversion of the fecal stream were performed in 15 of 42 of our patients with rectal, perineal or buttock wounds, where complete diversion was required (Table 4). Seventy-three per cent of these

TABLE 3. Postinjury Complications

Complication*	No. Patients	Per cent
Intra-abdominal abscess or empyema	16	35
Bowel obstruction	10	22
Stress ulcer bleed	5	11
Enterocutaneous fistula	5	11
Pancreatitis	2	4
Pneumonia	2	4
Malaria	2	4
Thrombophlebitis, lower extremity	2	4

*The postinjury course of patients with one or more complications is considered "stormy."

TABLE 4. *Indications for Colostomy*

Indication	No. Loop Colostomies
Colon Injury	62
Exteriorization	51
Proximal decompression	11
Rectal injury	9
Buttock and/or perineal injury	6

patients experienced a "stormy" post-injury course (i.e., with one or more of the complications listed in Table 3), whereas, 41% of those with complete diversion had a stormy course. This experience again re-affirms the dictum that a completely diverting double barrel colostomy is mandatory in the management of perforating rectal injuries.^{4,6,10,11,16,18}

Results

Simple loop closure was performed in 44 cases and resection with anastomosis was performed in 33 cases (Table 5). The indications for loop colostomy and the number of associated injuries were comparable for the two groups. Fifty per cent of those who had simple loop closure had had a stormy initial post-injury course while only 39% of those who had resection and anastomosis had had significant complications following their initial surgery. Choice of the loop closure procedure was left to the surgeon's discretion. Two attempts at simple loop closure were aborted in favor of resection and anastomosis because of edema of the bowel wall. Both of these patients had suffered multiple severe injuries. The average operating time for simple loop closure was 70 minutes compared to 115 minutes for resection and anastomosis. In 13 of the 44 simple loop closures, no nasogastric tube was used postoperatively, and in the other 31 patients, nasogastric suction was used an average of 2.8 days. Nasogastric intubation was used an average of 3.4 days in 28 of the 33 patients who had resection and anastomosis. The complication rate following simple loop closure was 9%. It was 24% following resection and anastomosis (Table 6). With simple loop closure the

TABLE 5. *Loop Colostomy Closure: Initial Indication for Colostomy*

	Simple Closure (44 cases)	Resection and Anastomosis (33 cases)
Exteriorization	27 (61%)	24 (73%)
Decompression	8 (18%)	3 (9%)
Diversion (Rectal, buttock or perineal injury)	9 (21%)	6 (18%)
Total	44 (100%)	33 (100%)

TABLE 6. *Complications Associated with Loop (Simple) Closure Versus Resection and Anastomosis*

Loop Closure (44 cases)	Resection and Anastomosis (33 cases)
Superficial wound infection (2)	Superficial wound infection (1)
Suture line leak and obstruction (1)	Deep wound infection, abscess (3)
Urinary tract infection (1)	Subdiaphragmatic abscess (1)
	Anastomotic leak (1)
	Urinary tract infection (1)
	Ureteral Calculus (1)
Total 4 (9%)	Total 8 (24%)

blood supply to the bowel edges is theoretically enhanced by maintaining continuity of the mesenteric wall. It could be argued that simple loop closure, when feasible, is a safer procedure than end-to-end anastomosis.

Discussion

The overall complication rate for the 77 cases of colostomy closure was 15.5%. Major complications involving the anastomosis occurred in 3.9% (Table 7). Although 87% of the wounds were closed primarily, the incidence of postoperative wound infection was only 7.6%. Patient age, and demonstrated ability to survive many severe injuries which were frequently complicated by sepsis, may have contributed to this low rate of infection. Another consideration is that colostomy closure was delayed until the patient had regained his lost weight and was considered to be in excellent condition. There were no deaths.

Our experience with simple closure of the loop colostomy compares favorably with the report by Thomson and Hawley¹⁴ who performed simple closure of transverse loop colostomies on 130 older patients with carcinoma or diverticulitis. They reported an incidence of 2.9% leakage and 17.2% wound infection. We had one significant complication in 44 single loop closures. The patient suffered a suture line breakdown which required a proximal diverting colostomy. The other three minor complications consisted of two wound infections and one urinary tract infection.

Goligher⁵ stated in reference to simple loop closure: "This operation has a notorious reputation for subsequent breakdown and leakage of faeces, but with a

TABLE 7. *Complications of Colostomy Closure in 77 Cases*

Complication	Number	Rate (per cent)
Leakage and/or obstruction*	3	3.9
Wound infection	6	7.6
Urinary tract infection	2	2.6
Ureteral Calculus	1	1.3

*One required new colostomy.

well-conducted closure this should seldom occur." Our results would bear out his optimism and establish this procedure as a safe and simple means of closure for the loop colostomy.

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Results of Ankle Systolic Pressure Measurements in Patients With Intermittent Claudication Being Treated With Clofibrate

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Ankle systolic pressure measurements in 67 patients with intermittent claudication treated with Clofibrate for an average period of 11 months and 32 untreated patients suggest that 1) patients with a raised initial plasma fibrinogen concentration have more severe disease than those with low initial plasma fibrinogen concentration and 2) the response to treatment with Clofibrate is significantly better in those with a raised plasma fibrinogen concentration. On the basis of the patients own estimation of their claudication distance there was marked symptomatic improvement in the treated patients. There was also a significant decrease in mean plasma fibrinogen levels in the treated patients and it is suggested that the hypofibrinogenemic effect of Clofibrate may be responsible for the benefit of this drug in patients with vascular disease.

RECENTLY Dormandy et al. reported the preliminary results of a clinical trial of Clofibrate in patients with intermittent claudication.⁴ The results suggested some clinical improvement in treated patients associated with a significant fall in whole blood viscosity and plasma fibrinogen levels.

Since the beginning of this trial we have started to study the ankle systolic pressures of the patients in the trial using a Doppler trans-cutaneous blood velocity detector¹⁰ and are now able to report the results of these studies in the treated and untreated groups after an average period of 11 months. Because previous evidence suggests that those patients with an elevated plasma fi-

brinogen concentration are most likely to have more severe disease and a worse prognosis^{5,6} we have subdivided the patients into two groups—those with a high, and those with a low initial plasma fibrinogen concentration.

We also report on the symptomatic progress of these patients up to the present time, assessed by change in claudication distance.

Patients

The 67 treated patients were drawn randomly from those attending a clinic for intermittent claudication and each received 2g of Clofibrate daily for an average period of 11 months.

The treated patients had an average age of 62 years and their symptoms had been present for a mean period of 32 months. Seventy five percent were men, 26% had a history of heart disease and three patients had diabetes mellitus. Seventy two percent were tobacco smokers.

The 32 untreated patients were selected to match as closely as possible the clinical characteristics of the treated group.

No patient had gangrene or pre-gangrenous changes.

Assessment of Patients

All patients were assessed clinically at the beginning of treatment and at two monthly intervals as already described by Dormandy.⁵

Since the start of the trial all patients have also under-

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TABLE 1. Summary of All Pressure Index Results Comparing Values in the Treated and Untreated Groups and Evaluating the Significance of Plasma Fibrinogen Concentration

	Mean Resting Pressure Index			Mean Post-Exercise Pressure Index			Mean Time Required for Post-Exercise Systolic Pressures to Return to Resting Level (in mins)		
	Treated		Untreated	Treated		Untreated	Treated		Untreated
All Patients	0.751 (SE=0.02)	N. S.	0.728 (SE=0.031)	0.471 (SE=0.382)	N. S.	0.411 (SE=0.078)	2.335 (SE=0.20)	N. S.	2.99 (SE=0.371)
Patients with initial fibrinogen concentration <400 mgs%	0.762 (SE=0.028)	N. S.	0.818 (SE=0.037)	0.49 (SE=0.053)	N. S.	0.696 (SE=0.052)	2.556 (SE=0.339)	N. S.	1.925 (SE=0.449)
	N.S.		P<0.02	N. S.		P<0.001	N. S.		P<0.01
Patients with initial plasma fibrinogen concentration >400 mgs%	0.742 (SE=0.293)	N. S.	0.674 (SE=0.037)	0.435 (SE=0.0603)	P<0.05	0.193 (SE=0.087)	2.379 (SE=0.238)	P<0.005	3.923 (SE=0.503)

SE=Standard Error; N. S.=Not Significant; The P numbers refer to the level of significance between the mean values for the patient groups shown in adjacent compartments of the Table.

gone measurement of the ankle systolic pressure of the affected limb by the method described by Yao et al.¹⁰ using a Parks' trans-cutaneous Doppler blood velocity detector. Measurements were made with the patient supine after a 30 minute rest period and then at 30 second intervals following a standardized period of exercise. The result was expressed as the pressure index, i.e. the ratio of the systolic ankle pressure to the systolic brachial artery pressure.⁹ A record consisting of three values was made for each patient: 1) the resting pressure index; 2) the post exercise pressure index immediately after completion of the exercise; and 3) the time required in minutes after the exercise for the ankle systolic pressure to return to the resting level.

The plasma fibrinogen concentration (PFC) was measured by heat precipitation and turbidimetric quantification.⁸ Estimates were made at the beginning of treatment and after an average period of 7.4 months. For the purpose of evaluating the effect of PFC on the ankle systolic pressure, results of the treated and untreated groups have been further sub-divided into those with high PFC if the value before treatment was 400 mgs% or more, and those with low PFC if the initial value was below 400 mgs%.

The preliminary results of clinical assessment of most of the patients in this trial have already been reported⁴ but we took this opportunity of assessing the patients own views on their progress by measuring the change in stated claudication distance. In order to eliminate as far as possible the errors of such a subjective estimate of progress we regarded a change in claudication distance as having occurred only if the logarithm of the distance in yards had changed by 0.3 or more. Results were expressed as better, unchanged or worse.

Results

All the pressure measurement data is shown in Table 1. The untreated patients with a high PFC had significantly lower resting and post-exercise pressure indices than those with a low PFC and also took significantly longer to regain the resting ankle systolic pressure level after exercise.

When the results in the treated and untreated group are compared it can be seen that although the treated group had higher resting and post-exercise pressure indices and took less time to regain the resting value after exercise the results did not reach a high level of statistical significance unless the patients with a high PFC alone were studied (Fig. 1). In this group of patients the improvement in the mean post-exercise pressure index and decrease in time taken to regain the resting pressure after exercise both

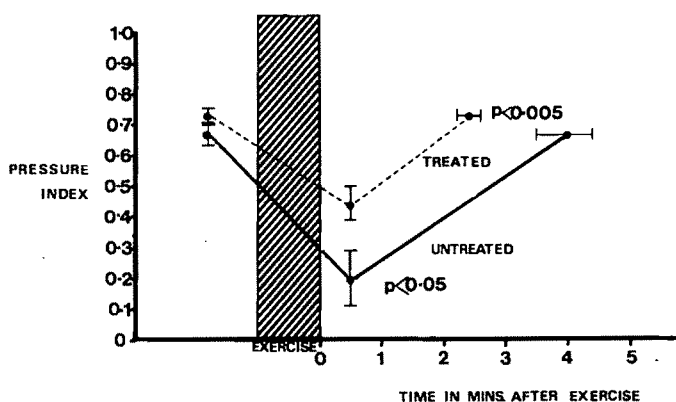


FIG. 1. Mean pressure index results in patients with high plasma fibrinogen concentration. (29 treated 13 untreated with initial plasma fibrinogen concentration above 400 mgs%)

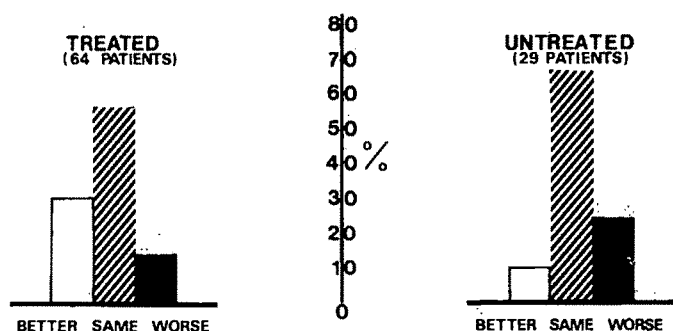


FIG. 2. Symptomatic progress assessed by change in claudication distance after 11 months.

reached significant levels in the treated compared with the untreated patients. ($P < 0.05$ and $P < 0.005$ respectively).

Results of symptomatic assessment measured by change in claudication distance are shown in Fig. 2. The percentage of patients that improved in the treated group was three times greater than that of the untreated group. The number of patients who improved in the treated group was significantly greater than the number who improved in the untreated group at the 5% level.

Dormandy has already reported the results of PFC estimations in the patients in this trial.⁴ During treatment the mean PFC fell from 420 mgs% (S.D. 116) to 330 S.D. 113) over the first 7.4 months of the trial. This represented a significant decrease ($t = 3.28$, $P < 0.01$), and was largely due to reduction of the abnormally raised PFC values found in a proportion of these patients with peripheral vascular disease. The mean PFC of untreated patients remained unchanged.

Discussion

Our findings in this preliminary trial of Clofibrate in patients with intermittent claudication suggest that during an 11 month period there was an improvement in the mean post-exercise pressure index and the mean time period required for return of the post-exercise ankle systolic pressure to the resting level. This improvement was especially significant in the group of patients with an initial PFC above 400 mgs%.

These changes were accompanied by a significant fall of mean PFC during the trial period. The ankle systolic pressure results of patients in the untreated group also suggest that patients with a high PFC have a significantly lower mean resting pressure index. ($P < 0.02$) and mean post-exercise pressure index ($P < 0.01$) than patients with a low PFC. The post-exercise pressure index of these untreated patients with a high PFC also takes a significantly longer time to return to the resting level ($P < 0.01$) than those with a low PFC.

There was also a significant symptomatic improvement

in the treated patients assessed by change in claudication distance.

Previous work by Dormandy et al.⁶ has shown that the severity and prognosis of disease in patients with intermittent claudication is related to the PFC and the reason for this relationship may be that the raised blood viscosity of patients with high PFC results in a decreased blood flow through the diseased arteries.³

Earlier results reported elsewhere⁴ on this trial of Clofibrate suggest a significant improvement in treated patients as assessed by improvement in plethysmographic blood flow patterns. Plethysmography, however, is a time consuming method of investigation and not suited to a large trial. We have, therefore, begun to measure the ankle systolic pressure before and after a standardized exercise period and to measure the time required for the post-exercise level to return to the resting value. These methods have been shown to give a good indication of the severity of peripheral vascular disease.⁷

It is also known that Clofibrate decreases the raised PFC found in a proportion of patients with peripheral vascular disease¹ and it would be reasonable to postulate that those patients with raised PFC might benefit most from Clofibrate treatment.

The results described in this paper provide confirmation that untreated patients with a high PFC have more severe disease and also suggest that the patients with a raised PFC at the commencement of treatment responded better to Clofibrate treatment over an average period of 11 months as assessed by ankle systolic pressure studies, and that the mean PFC was significantly reduced during the first 7 months of this period.

We also report the results of the patients own symptomatic assessment of change in their claudication distance. We have attempted to rule out discrepancies due to patient error and due to disproportionately large changes of long claudication distances by considering only those patients who had a change in the logarithm of claudication distance in yards of 0.3 or more. However, claudication distance remains a crude indication of clinical prognosis and we do not wish to over-stress the importance of these results.

Clofibrate has also been shown to be effective in certain patients with ischaemic heart disease in a large double blind trial.² It is interesting that the beneficial effect was not found to be related to the well established hypolipemic activity of this drug, and recent data reported by Dormandy et al.⁶ suggests that the altered lipid biochemistry in many patients with intermittent claudication is not related to the severity or prognosis of the disease. It would appear, therefore, that the beneficial effect of Clofibrate in vascular disease is unlikely to be associated with alteration of the plasma lipids.

The results in this paper suggest that the hypofibrinogenemic effect of Clofibrate may be related to the improvement in patients with peripheral vascular disease. In order to establish the clinical value of Clofibrate in intermittent claudication and the importance of the biochemical effects of this drug there is need for a double blind trial.

Acknowledgments

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Soft Tissue Sarcomas

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One hundred fifty-five adult patients with "operable" soft part sarcomas including rhabdomyosarcoma, liposarcoma, leiomyosarcoma and fibrosarcoma of the trunk and extremities are reviewed. Local recurrences of 93% and 60% occurred after local and wide excisions of the primary tumor. In this series of patients, amputation was the most efficient procedure for controlling the primary site. The absolute 5 and 10-year survival rates for all four groups of tumors were 50% and 26%. Development of a second primary tumor of a different cell type occurred in 9% of the patients. Local recurrence, single distant metastasis, and/or second primary tumors should be considered potentially curable and appropriate surgical and/or radiation therapy carried out.

SOFT TISSUE SARCOMAS are infrequent neoplasms which often develop insidiously, and frequently present problems for both the pathologist in histologic classification and subsequently, the clinician in their management. Several factors are decisive in the initial selection of the most appropriate surgical procedure.

This report reviews our experience with 155 adult patients with operable soft tissue sarcomas treated at the Roswell Park Memorial Institute during the years 1950 through 1972.

Methods

The 155 patients included 40 with rhabdomyosarcoma, 40 with liposarcoma, 41 with fibrosarcoma and 34 with leiomyosarcoma of the soft somatic tissues of the trunk and extremities. Not included were tumors originating in the retroperitoneal tissues, genitourinary tract, and the head and neck areas, since the nature and surgical problems of sarcomas at these anatomical sites may be different.

Tumor recurrences confirmed by histological examination or by clinical studies were divided into the following categories: 1) *local*—referring to a recurrence within the previous surgical site or the immediate adjacent tissues;

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and 2) *distant*—defined as a recurrence in any site other than those tissues or muscle group of origin for the primary site, such as the lungs, central nervous system, viscera, and skeleton. A majority of the histological slides from all 155 patients were reviewed by Dr. John Pickren, Chief Pathologist at Roswell Park Memorial Institute, and co-author of this paper.

Five types of operations were used for treating the primary tumor depending on its size and anatomic site, namely: 1) radical amputation—defined as forequarter, hindquarter, or a disarticulation of the extremity at the hip or shoulder joint; 2) major amputation—removal of a major portion of an extremity such as above the knee or below the knee amputation; 3) wide excision—excision of the tumor with a three centimeter or more margin of normal tissue; 4) local excision—removal of the tumor with the "pseudocapsule" or less than one centimeter of normal tissue; and 5) local excision followed by a wide reexcision—excision of the previous surgical scar and a three centimeter area of normal tissue surrounding the area of the previous locally excised tumor, performed within 4 to 8 weeks of the local excision.

Clinical Manifestations

In this group of 89 males and 66 females, the age at the time of diagnosis ranged from 16 years to 80 years with a majority occurring between the ages of 40 and 70. These sarcomas presented as a painless enlarging mass in 120 of the 155 patients. In those patients presenting with pain, the pain was usually late in appearance and often mild in character.

The duration of the tumors before the patient sought medical attention varied from a maximum of 10 years to a minimum of 2 weeks, with an average period of 42 weeks. There was an average delay of 6 weeks before the defini-

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TABLE 1. Anatomic Location of 155 Soft Tissue Tumors

Histologic Type	Shoulder-Upper Arm	Lower Arm-Hand	Trunk	Hip-Upper Thigh	Above Knee-Foot	Total # Patients
Rhabdomyosarcoma	4	3	5	17	12	41
Liposarcoma	4	4	8	10	14	40
Fibrosarcoma	6	4	9	11	10	40
Leiomyosarcoma	6	4	8	6	10	34
Total # Patients	20	15	30	44	46	155

tive surgical procedure was performed. This delay is explained in part by the referral pattern of this Institute and multiple pathological consultations concerned with histological classification. Forty-five patients had two or more tissue diagnoses such as liposarcoma and fibrosarcoma, or rhabdomyosarcoma, leiomyosarcoma and undifferentiated sarcoma. In some instances the pathologist requested a second or third biopsy specimen.

The anatomic location of these 155 tumors is outlined in Table 1. The lower extremity was the prominent site in 90 patients for all 4 tumor groups.

Measurements of the primary tumor at the time of diagnosis were documented in 88 of the 155 patients; the smallest tumor was 1 x 1.5 cm and the largest was 12 x 28 cm. The average diameter of the tumors was 7 x 8 cm which illustrates dramatically the absence of pain which might prompt an earlier search for care. It is equally disturbing to find that the tumors in recent patients were as large, and the delay of treatment the same, as in those patients treated earlier in the study period.

Treatment and Results

For these 155 patients with soft tissue sarcomas, the 5 and 10-year absolute survival rates following all forms of therapy (which included surgery for the primary tumor

and subsequent local and/or distant recurrences, and chemotherapy and/or radiation therapy for disseminated disease) are outlined in Figure 1. The 5 and 10-year average survival for all 4 tumor groups was 50% and 26%. For each individual group, the respective 5 and ten-year survival rates were: liposarcoma—65% and 28%; fibrosarcoma—55% and 38%; leiomyosarcoma—47% and 17%; and rhabdomyosarcoma—31% and 20%. Of interest are 27 patients (6 with fibrosarcoma, 9 with liposarcoma, 6 with rhabdomyosarcoma, and 6 with leiomyosarcoma) living with no evidence of tumor beyond 10 years and up to 20 years.

The frequency of local and distant recurrences following the various surgical procedures for the primary lesion is summarized in Table 2. The pattern and recurrence rates, both local and distant, were similar for each of the 4 groups of tumors. Local recurrence occurred in 54 (93%) of 58 patients after *local* excision of the primary lesion and in 16 (73%) of 22 patients following wide re-excision of the primary area of a previously locally excised lesion. Local recurrence developed in 15 (60%) of 25 patients following *wide* excision of the primary lesion. Thirty-eight patients had major and/or radical amputations as the initial definitive surgical procedure for the primary tumor and failure to control the primary lesion occurred in 3 (8%) of these patients.

Nine patients received radiation therapy to the primary area following local excision of the primary tumor, and a local recurrence occurred in 4 (45%) of these patients. Two patients treated with radiation following wide excision of the primary lesion did not develop local recurrence.

Subsequent recurrences following surgical treatment of the first local recurrence are summarized in Table 2. A local recurrence occurred following local excision of the recurrent tumor in 29 of 33, or 88% of the patients; in 19 of 35, or 54% of the patients treated by wide excision; and in 2 of 11, or 18% of the patients treated by major and radical amputations.

Of the 155 patients, 121 had recurrent disease. The first recurrence was local only in 83 patients, distant in 29 both local and distant in 9. The fate of these patients is interesting. Of the 83 with local recurrences, several patients had two or more subsequent surgical procedures:

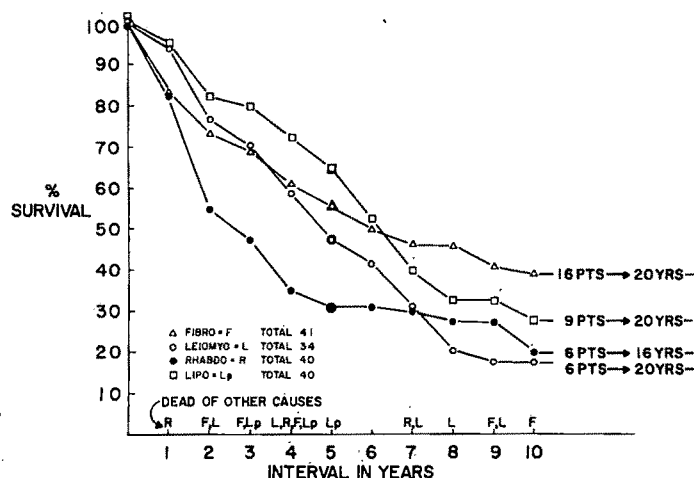


FIG. 1. This figure illustrates the absolute 5 and 10-year survival for each of the 4 types of soft tissue sarcomas following the initial treatment and all subsequent surgical procedures and other treatment, such as chemotherapy and radiation therapy.

TABLE 2. First Recurrence Following Various Surgical Procedures for the Primary Tumor of Soft Tissue Sarcomas

Surgical Procedure	# Pts	Fibrosarcoma			Leiomyosarcoma			Rhabdomyosarcoma			Liposarcoma			Total LR	
		LR	DR	Both*#Pts	LR	DR	Both*#Pts	LR	DR	Both*#Pts	LR	DR	Both*		
LE	19	16(89%)**	2	1	15	12(93%)**	—	2	9	9(100%)	—	—	15	15(100%)	54/58 93%
LE → WE	4	3(75%)	—	—	8	4(50%)	1	—	7	6(100%)**	1	1	3	2(67%)	16/22 73%
WE	8	3(38%)	2	—	5	3(60%)	—	—	7	3(71%)**	1	2	5	2(60%)**	15/22 60%
Amp	5	—	3	—	3	1(67%)**	—	1	3	(33%)**	—	1	5	—	3/16 8%
Rad Amp	4	—	2	—	2	—	—	8	—	4	—	—	8	5	—
LE → RT	—	—	—	—	—	—	—	6	3(50%)	2	—	3	1(33%)	—	4/9 45%
WE → RT	1	—	—	—	1	—	1	—	—	—	—	—	1	—	—

Recurrences Following Surgical Treatment of the First Local Recurrence															
LE	13	12(100%)**	—	1	6	4(83%)**	1	1	4	3(100%)**	—	1	10	6(70%)**	29/33 88%
WE	6	2(50%)**	1	1	11	2(45%)**	4	3	9	4(56%)**	3	1	9	4(67%)**	19/35 54%
Amp	1	—	1	—	—	—	—	—	1	—	—	—	1	—	—
Rad Amp	—	—	—	—	3	—	—	—	4	1(50%)**	2	1	1	—	2/11 18%
LE → RT	1	—	—	—	—	—	—	—	3	—	3	—	—	—	—

LR = local recurrence
DR = distant recurrence

LE = local excision

WE = wide excision

Amp = amputation

Rad Amp = radical amputation

LE → WE = local excision followed by wide excision

LE or WE → RT = local or wide excision followed by radiation

* Both = simultaneous local and distant recurrences

** % includes local recurrence of those patients with both local and distant recurrences

(local or wide excisions, or amputations) in an attempt to control the tumor at the primary site. The 5-year survival rates following surgical treatment of the first and/or all subsequent local recurrences were as follows: liposarcoma, 53%; fibrosarcoma, 43%; leiomyosarcoma, 53%; and 24% for rhabdomyosarcoma.

The first detectable recurrence was distant in 29 patients, the lung being the most common site of these metastases. Only two of these 29 patients survived more than 5 years; both patients are living free of disease for 15.9 and 17 years, respectively.

The first recurrence occurred simultaneously in local and distant sites in 9 patients. Of these 9, 4 died in less than 6 months and the other 4 died within 3.5 years from progression of disease.

A distant recurrence occurred in 38 or 24% (29 distant only, and 9 with both local and distant) of the 155 patients following the initial surgical treatment of the primary lesion. The incidence of distant recurrences following subsequent surgically treatable first, second, third and fourth recurrences were 30/83 (36%), 9/36 (25%), 4/15 (27%), and 3/8 (38%), respectively. In other words, persistence in providing adequate surgical excision of recurrent lesions is still successful in nearly two-thirds of the patients.

The time interval until the appearance of the first local recurrence following surgical therapy of the primary tumor is outlined in Fig. 2. Of the 155 patients, local recurrence occurred in 83 patients and of these, 71% were detected within one year and 82% within the first two years. However, prolonged followup is necessary,

since the first local recurrence without evidence of distant disease occurred in one patient 10 years following the initial wide excision of a liposarcoma of the thigh. This patient has remained free of further recurrences for more than 3 years, following a wide excision of the local recurrence.

There are apparently various host factors which influence survival and Table 3 illustrates the variant biological interaction of rhabdomyosarcoma in two patients. The first patient, J.R., a 56-year-old Caucasian man, had 11 local recurrences, each treated by local excision during a period of 4.3 years following local excision of the primary tumor in the pectoral muscle. The twelfth recurrence was treated by a forequarter amputation. Subsequently, three local recurrences developed in the amputation site during the next 11 years and were treated by wide local exci-

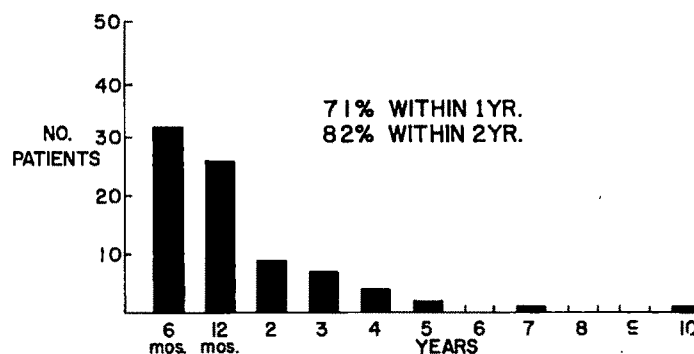


FIG. 2. This diagram illustrates the time interval until local recurrences were detected following the initial surgical treatment of the primary lesion. Seventy-one per cent occurred within one year.

TABLE 3. Variant Biological Interaction of Rhabdomyosarcoma and the Patient

Case Hx J.R. 56 W.M. Site-Pectoral Muscle	Case Hx M.M. 66 W.M. Site-Anterior thigh
Local Excision (1/25/53)	Biopsy (5/17/54)
4 Yrs. 3 Mo. ↓ 11 Separate local recurrences and local excisions	Hip disarticulation 5/18/54
12th Local recurrence 4/2/57	1st Recurrence Distant-pulmonary 5-Mo.
Forequarter amputation 5/14/57	
10 Yrs. 11 Mo. ↓ 3 Local recurrences and wide local excisions	Died disease 1/1/55 Since Dx 7 Mo.
Pulmonary Metastasis 4/15/68	
7 Mo. ↓ Died disease 8/5/68 Since Dx 15 Yrs. 8 Mo.	

sions. In 1968, pulmonary metastases were detected followed by progression and death 15.8 years after the initial diagnosis.

The second patient, M.D., a 66-year-old Caucasian man, had a hip disarticulation for a large primary rhabdomyosarcoma in the upper anterior thigh. The first evidence of recurrence was pulmonary metastases at 5 months, later followed by rapid progression and death only 7 months from the time of initial diagnosis.

Forty of the 155 patients underwent radical amputations as the treatment for the primary tumor and/or for subsequent local recurrences, and the survival rates for these patients are summarized in Table 4. These procedures were an integral part of the primary treatment in 23 of the 40 patients. The 5 and 10-year survival rates for these 23 patients including all 4 tumor groups was 43% and 19%. These procedures were performed on 17 patients for recurrences and the 5 and 10-year survival rates from the time of initial diagnosis was 67% and 34%, and from the time of the radical surgical procedure, 47% and 34%. The average 5 and 10-year survival rates for all 40 patients from the time of initial diagnosis was 45% and 26%, respectively.

In this study, residual tumor was confirmed in specimens from 17 of 43 patients, or 40%, who had wide re-excision of recent locally excised tumors. Fifty-two patients had surgical procedures which provided tissue of lymph node bearing areas for histological study. Invasion of lymph nodes by tumor appeared to be a late manifestation of the disease and was confirmed in only 6 (12%) of these 52 patients. In this group, 8 patients were diagnosed by physical examination as having clinically positive nodes, but tumor invasion was confirmed by histologic studies in 2 of the 8 patients.

Fourteen of the 155 patients, or 9%, developed a second primary tumor of a different cell type and these second primary tumors are summarized in Table 5. Of these 14 patients, 4 are living free of disease from 6 to 15 years following surgical treatment for both primary tumors.

Survival following dissemination or an unresectable state of these sarcomas was short, as outlined in Fig. 3. Of 82 patients with disseminated disease treated with

TABLE 4. Survival of Sarcoma Patients Following Radical Amputations

Surgical Procedure	# Pts.	Treatment for Primary Lesion Survival	Treatment for Subsequent Local Recurrence Survival from Time of Amputation
Hemipelvectomy	13	6 died disease 10 mo to 1.8 yrs 1 died no tumor (coronary) 3 yrs 1 living NED* 4.6 yrs 5 living NED > 5 yrs (2/5 pts. living NED > 10 yrs)	5 3 died disease 1 yr to 3.4 yrs 1 died no tumor 3.6 yrs 1 died disease 8.7 yrs
Forequarter	4	1 died disease 5.5 yrs 1 living NED 9.3 yrs 1 living NED 11 yrs 1 living NED 16.4 yrs	10 3 died disease 4 mo to 3.4 yrs 1 died no tumor (CVA) 10.8 yrs 1 died disease 11.3 yrs 1 died disease 14 yrs 1 living NED 2.2 yrs 3 living NED > 5 yrs (2/3 > 10 yrs)
Disarticulation	6	4 died disease 7 mo to 1.3 yrs 1 died post-op CVA 1 mo 1 living NED 2 yrs	2 1 died disease 7 mo 1 living NED 3.8 yrs
Total	23	5 yr survival rate 43%** 10 yr survival rate 19%**	Total 17 5 yr survival rate 47%** 10 yr survival rate 34%**

*NED = no evidence of disease

**Does not include two patients living NED < 5 years.

TABLE 5. *Second Primaries of Different Cell Type*

# PATIENTS	SITE OF TUMOR
6	G.I./or Biliary Tract
4	Breast
2	Brain
2	Urinary Tract
14/155 Patients (9%)*	

*4/14 Pts. living 6-15 years

chemotherapy and/or radiation therapy, 65 or 80% of these patients were dead within one year.

Comment

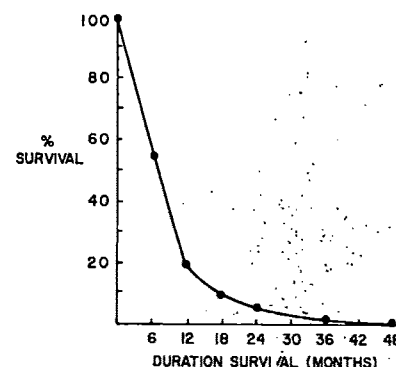
Soft tissue sarcomas are difficult malignancies to control at the primary site.^{2,3,8,9} This series of 155 patients re-emphasizes this problem by a local recurrence rate of: 1) 93% after local excision of the primary lesion; 2) 88% following local excision of the first surgically treatable local recurrence; and 3) an average 53% following all initial surgical therapies for the primary lesion. This Institution provides consultation and therapy for many patients and this high incidence of local recurrence is a reflection of the referral pattern of the Institute. Even so, figures of 93% and 88% illustrate the futility of repeated local excisions as adequate operations when there is still a chance of cure.

Failure of "conservative" local excisions would be anticipated by the histologic confirmation of residual tumor in specimens from 17 of 43 patients (40%) who had wide re-excisions of recently locally excised lesions. The incidence of local recurrence in patients with wide re-excisions was 73%. This figure of 73% and a local recurrence rate following initial wide excision of the primary lesion of 60% indicates the need for more radical procedures, since these malignancies characteristically have direct extension of neoplastic cells for long distances along muscle and nerve bundles and fascial sheaths.

In this series, amputation was the most efficient procedure for controlling the primary site. The initial definitive surgical treatment of the primary tumor was a major and/or a radical amputation in 38 patients. Of these 38 patients, only 3 patients (8%) developed a local recurrence. Of the 83 patients with a first local recurrence, 11 patients were treated by amputations (major and radical) and 2 (18%) of this group developed local recurrence. Although this group is small, the 18% incidence of local recurrence following major amputations for subsequent recurrences indicates the increasing difficulty of controlling the primary lesion.

In addition, failure to control the tumor at the primary site by the first operation affects the overall prognosis, since in this series there was an approximate 30% incidence of distant metastasis occurring following all subsequent treatable local recurrences.

FIG. 3. This figure illustrates the survival of 82 patients with soft tissue sarcomas following an unresectable state treated with chemotherapy and/or radiation therapy.



This series of patients with soft tissue sarcomas illustrates, as others have reported^{4,9,11,16} several specific surgical principles and techniques which must be followed to achieve maximal long-term survival and cure, namely: 1) an adequate biopsy of every persistent soft tissue mass for histologic evaluation. The biopsy may be by excision if the tumor mass is small, or by core needle, or incision. The biopsy site should be placed within an area which will be included in a definitive cancer operation and the specimen should be given immediately to the pathologist for (a) confirmation that adequate tissue was removed for study and (b) when feasible, a histologic diagnosis by frozen section. 2) If a definitive diagnosis can be made by frozen section, proceed with the previously planned radical surgical excision of the lesion. However, if any uncertainty exists as to the diagnosis of an initial lesion by frozen section, the biopsy wound should be closed and the definitive surgical procedure delayed until after study of paraffin sections. 3) The operative procedure must be based on several factors such as anatomic location, size of lesion, depth of invasion, and fixation or nonfixation to vital structures. When an adequate 5-6 cm three dimensional margin of normal tissue cannot be removed, then, in general, amputation proximal to the effected limb segment is best. A forequarter or hemipelvectomy would appear to offer the best hope for cure in those patients with deep lesions, without evidence of distant metastasis, in the upper thigh, groin, buttock, and shoulder areas. 4) Local recurrence without distant spread should be considered potentially curable and proximal amputation is indicated whenever feasible. Lesser procedures performed following local recurrences must be considered more radical and entail more risk to the patient. 5) Growth of tumor tissue in lymph nodes appears to be a late phenomenon and, therefore, prophylactic excision of the regional nodes is unnecessary unless the primary lesion is in juxtaposition (10-15 cm) to them. 6) Patients with soft part sarcomas should have an examination and chest x-ray at 3 month intervals for the first 2 years, then every 6 months through the first 10 years, and yearly thereafter for detection, of local or distant recurrent disease and/or second primaries. 7) Local recur-

rences may occur after disease-free intervals or more than 10 years. These and single distant recurrences, or second primaries, should be considered potentially curable and appropriate therapy carried out.

Radiation Therapy

Our experience with postoperative adjuvant radiation therapy is limited and cannot be evaluated. Various degrees of tumor regression and pain relief were observed in several of our patients with non-resectable liposarcoma and embryonal rhabdomyosarcoma.

Several retrospective studies provide evidence that soft tissue sarcomas in many patients are responsive to radiation therapy.^{6,10,12,13,15,17} The cure rate following combined treatment with radiation and surgery was significantly higher than that observed with only surgery.^{10,17} Amputation of extremities was avoided in several of these patients.¹⁷ These data support the need for prospective clinical studies of combination therapy.

Chemotherapy and Immunotherapy

Thirty-six of the 155 adult patients received chemotherapy for disseminated disease. These agents included dactinomycin, cyclophosphamide, vincristine, nitrogen mustard, thio-tepa, and cytosine arabinoside administered singly or in combination without a clinically significant antitumor effect. Several recent reports^{1,5,18} indicate antitumor effect of adriamycin used alone or in combination with dimethyl triazeno imidazole carboxamide. Prognosis of children with solid tumors has been significantly improved with a combination of surgery, radiation, and maintenance multiple chemotherapy.^{7,14} These reports are encouraging and further studies of multimodality therapy may improve the overall survival rates of adult patients with soft tissue sarcomas.

The risk of dangerous immunosuppression with chemotherapy must be balanced against the theoretical destruction of residual tumor cells. Immunotherapy

rarely provides spectacular tumor regressions but it can be used as an adjuvant to local therapy with undue risk.

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Lung Thermal Volume in Pulmonary Edema: Effect of Positive End Expiratory Pressure

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Effects of intermittent (IPPB) and positive end-expiratory pressure (PEEP) ventilation on accumulation of pulmonary edema were compared, in dogs, after infusion of oleic acid. Pulmonary extravascular water was approximated as lung thermal volume (LTV), a double indicator method based on differential transit time for simultaneously injected right-to-left conductivity and thermal pulses. LTV was found to be decreased in animals treated with PEEP. The possibility that observed LTV changes reflect only the effect of PEEP on flow distribution, not lung water, was examined by alternating PEEP and IPPB; short-term changes in LTV did not occur. Mean values of other factors influencing pulmonary water transfer, e.g., pulmonary capillary wedge pressure, serum protein, arterial blood gasses, were not significantly different with or without PEEP. It was concluded that, for the oleic acid lesion, PEEP effects a small reduction in the rate of accumulation of pulmonary edema.

VENTILATION with positive end-expiratory pressure (PEEP) improves gas exchange in experimental pulmonary insufficiency.¹³ In man, PEEP is an accepted treatment when intermittent positive pressure ventilation (IPPB) does not achieve satisfactory arterial oxygen saturation at an acceptable inspired oxygen concentration.

Pulmonary insufficiency in surgical patients, while often of mixed or uncertain etiology, is characterized

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functionally by atelectasis, venous admixture, and edema. PEEP may influence all of these. Its favorable effects include increased functional residual capacity, tending to prevent small airway and alveolar collapse when interfacial forces are abnormal. Its effect on edema is less certain. Pulmonary extravascular water (PEVW) has been found both increased⁴ and unchanged^{1,8} by PEEP. The question of PEEP's effect on pulmonary extravascular water is clouded by three problems: incomplete understanding of the mechanism of edema formation in the lungs, lack of a completely satisfactory animal model of clinical pulmonary insufficiency, and the difficulties associated with in vivo measurement of PEVW. Measurements by the Chinard double indicator method³ account for only about 60% of the water that can be found by direct weighing, require large sampling volumes, and are not frequently repeatable. A recently introduced variation employs thermal and conductivity indicators^{2,11} to measure lung thermal volume (LTV). Frequent repetition is possible and correlation with weighed lung water reasonably good. The purpose of this study is to compare changes in LTV, with and without PEEP, in dogs with pulmonary insufficiency induced by oleic acid.

Methods

Two sets of experiments were done using 12 dogs. Lung damage was induced by infusion of oleic acid (0.1 ml/kg) into the pulmonary artery. Of the ten dogs used in the first set of studies, five were treated with PEEP, five with intermittent positive pressure breathing (IPPB). Serial measurements of lung thermal volume (LTV) were made in all.

Each animal was anesthetized with pentobarbital (30 mg/kg IV). An esophageal balloon was placed, orotracheal intubation performed with a cuffed side-tap tube,

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a Swan-Ganz catheter floated into the pulmonary artery, and the thermistor-conductivity catheter passed from femoral artery to infradiaphragmatic aorta. Pressure measurements were made with appropriate strain gauges. Dogs in the IPPB group were ventilated with a Harvard respirator set for a 15 ml/kg tidal volume. For the PEEP group the respirator outflow tube was placed under water to maintain end expiratory airway pressure at 10 cm H₂O. The dogs were in the right lateral position except during oleic acid infusion. When the animals were stable on the ventilator, control measurements were made of LTV, esophageal, arterial, pulmonary artery, and pulmonary artery wedge pressures; blood samples were taken for arterial blood gas tension and total plasma protein. Then, with the animals supine, oleic acid (0.1 ml/kg in four minutes) was injected into the right atrium. After 5 minutes the animal was returned to the lateral position. For the next 2 hours, LTV was measured in triplicate every 20 minutes, pressures every 30, and blood sampling repeated hourly. Supplemental oxygen was given some dogs in the IPPB group ($F_1O_2 < 50\%$) to avoid extreme hypoxemia. After two hours the dogs were sacrificed by injecting 20mEq of KCl into the right atrium. The chest was opened, the bronchi clamped, and the lungs removed and drained of blood by gravity. The lungs were weighed, dessicated to constant weight, and the weight difference taken to be weighed lung water (WLW).

In the second experiment, two dogs were used to determine whether rapid changes in LTV occur after end expiratory pressure is increased. It was reasoned that the smaller LTV associated with PEEP in the first group of animals might reflect changes in regional perfusion of the lungs. Experimental conditions were the same except that periods of IPPB and PEEP were alternated; LTV was measured frequently after each transition.

LTV, in all instances, was measured by injection of 10ml of room temperature NaCl solution into the right atrium. Dilution curves for temperature and conductivity were sensed by the thermistor and conductivity cells at the tip of the arterial catheter and recorded on analogue magnetic tape. Mean transit time for each indicator was calculated; their difference, less thermistor time constant, was multiplied by cardiac output obtained from the thermal dilution curve to give lung thermal volume.

Mean LTV in each group was examined for difference using Student's *t*-test. Regression equations were developed for LTV from control to 120 minutes and the slopes evaluated by analysis of covariance.

Results

Gross and microscopic examination of the lungs showed marked hemorrhagic edema. Pulmonary capillary wedge pressure remained low. Mean wedge pressure

($\pm$ SEM) for IPPB dogs was 6.5 ± 0.6 cm H₂O at two hours; with PEEP, it was 7.6 ± 2.6 . These group means were not significantly different by Student's *t*-test and no difference was found by covariance analysis. Significant intergroup differences were not found for serum protein initially 5.5g% in the IPPB group and 5.4 in the PEEP group, falling to 4.8g% in both at the end of the experiment. Mean arterial PO₂ for the two groups was not significantly different (supplemental oxygen was used with the IPPB group).

Figure 1 shows the observed sequence of changes in cardiac output and LTV. After one hour, cardiac output tended to be lower in PEEP, but the difference was not significant.

Measurements of LTV were at first normal and identical in both groups. Divergence began after 20 minutes (Fig. 1). Mean values at two hours were 18.5 ± 3.2 ml/kg for PEEP and 22.5 ± 2.6 for IPPB. Covariance analysis of the regression of values from control to 120 minutes showed differences both in slope ($P < 0.05$) and in mean values ($P < 0.001$).

Mean weighed lung water, expressed as g per kg body weight, was 19.2 ± 0.6 for IPPB and 19.9 ± 1.6 for PEEP. No correction was made for intravascular water.

Figure 2 shows results from the second group of experiments where LTV was measured while ventilation was changed from IPPB to PEEP and back to IPPB. The expected pattern of change in LTV was seen: a small decrease early after oleic acid infusion followed by more or less linear rise to values greater than twice control. However, rapid changes in LTV with changes in ventilator conditions were not seen.

Discussion

Pulmonary extravascular water was the variable of interest in these experiments but lung thermal volume was the variable actually measured. The correlation of LTV with weighed lung water is good ($r = 0.99$) when the two are compared in canine lungs made edematous by Dextran and epinephrine.² Direct validation of LTV as a measure of WLW is not as easy for lungs with the hemorrhagic lesion produced by oleic acid infusion. This model of pulmonary insufficiency was used here because it is a closer analogue of the low pressure pulmonary edema commonly treated with PEEP. A problem associated with use of this model is difficulty in correction of wet weight differences for residual intravascular water. The usual method for correction is tissue hemoglobin determination, not reliable when the lung contains extravasated red cells. In the present experiments the mean values of WLW for the PEEP and IPPB groups were not significantly different, but without correction these weights are imprecise and do not of themselves allow any conclusion as to the effects of PEEP on PEVW.

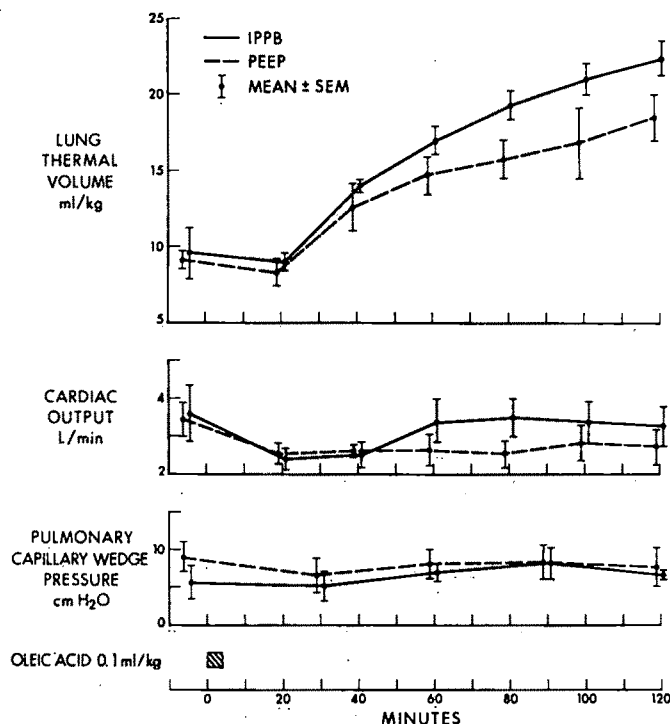


FIG. 1. Mean ($\pm$ SEM) values for each group. LTV begins to increase 20 minutes after injection; the increase is larger in the IPPB group. Cardiac output tends to be lower in the PEEP group, but the difference not significant.

Interpretation of measurements of LTV depends on the degree to which they approximate PEVW. They are not identical. One source of error is inclusion of nonaqueous tissue in LTV; it is small and should be the same in both groups of dogs.

Another systematic error might be caused by variation

in regional flow. No double indicator technique detects water in nonperfused areas of the lung. Although the data of Fig. 1 show LTV to be greater with IPPB than with PEEP, the difference could be only apparent if flow distribution is changed by PEEP. However, if the difference is due to changes in perfusion, alternating PEEP and IPPB should cause rapid reversible changes in LTV. No short time constant changes were seen in the data of Fig. 2, and although it is likely that larger variations in airway pressure or cardiac output might change LTV without real change in lung water, under the conditions of this experiment their effect appears to be small, leading us to conclude that for dogs with the oleic acid lesion, formation of pulmonary edema is retarded by positive end-expiratory pressure.

Several mechanisms can influence movement of water across pulmonary capillaries. The Starling hypothesis states that water transfer follows the balance of osmotic and hydrostatic pressures; it remains a hypothesis because not all forces involved are directly measurable, particularly the osmotic and hydrostatic components of interstitial pressure and the pressure within the pulmonary capillary. Guyton⁷ first suggested that interstitial hydrostatic pressure is negative, demonstrating it in dogs with implanted subcutaneous capsules.⁶ He further showed that in edematous tissue interstitial pressure increases at least 6-9 mmHg.⁵ Levine¹⁰ produced pulmonary engorgement and edema in dogs by changing pulmonary capillary hydrostatic and oncotic pressures, and then calculated normal pericapillary hydrostatic pressure to be -9 mmHg. PEEP increases FRC and hence increases interstitial pressure; this mechanism would favor movement of water out of the lungs.⁹ PEEP, however, also increased intrapleural pressure, which may change

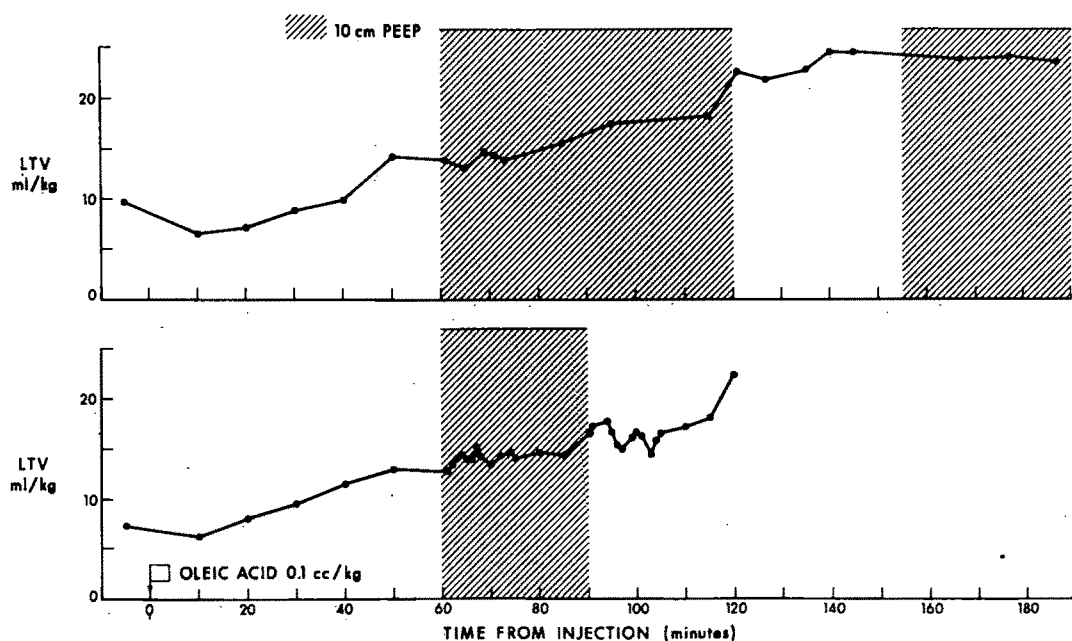


FIG. 2. Sequential measurement of LTV made in 2 dogs, both maintained on IPPB except during intervals shown hatched: here, 10 cm H₂O end-expiratory pressure was added.

the dynamics of pulmonary transfer in several other ways. Permutt¹² observed increased pulmonary capillary pressure with positive breathing; he likened flow from these relatively high pressure vessels to the low pressure left atrium to a waterfall. If respiratory conditions allow transmission of pulmonary venous hypertension to the pulmonary capillary, then pulmonary interstitial pressure should tend to increase. Effects on the right heart, notably reduced right atrial filling, are usually emphasized in explaining the circulatory effects of PEEP, possibly because small pressure changes seem most significant in a low pressure system. Permutt has called attention to an additional mechanism resulting from increased intrapleural pressure effects on the left heart, pointing out that if intrapleural pressure is less negative, transmural pressure is decreased; with reduced left ventricular afterload left atrial pressure falls, and to the extent that left atrial pressure is transmitted to the pulmonary capillary the hydrostatic gradient for water transfer changes toward reduction of lung water. In other words, a rationale can be found for either increased or decreased lung water with PEEP; in the model used here, it appears to effect a small reduction.

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Influence of Increased Circulating Levels of Splanchnic Lysosomal Enzymes on the Response to Myocardial Ischemia

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The ability of increased circulating activities of lysosomal hydrolases to disrupt myocardial cellular membranes was studied in anesthetized cats. Increased activities of lysosomal hydrolases were achieved by splanchnic artery occlusion (SAO) shock or by infusion of liver extract (LE). Myocardial ischemia (MI) was produced by ligation of the left coronary artery. Coronary artery ligation resulted in sustained S-T segment elevation associated with significant increases in plasma creatine phosphokinase (CPK) activity within 5 hours. Combination of SAO or LE infusion did not modify the increase in either the plasma CPK activity or the S-T segment following MI. However, SAO shock or infusion of LE increased CPK loss from normal and ischemic myocardium, the loss being greater when MI was combined with infusion of LE or SAO shock. Similarly, MI plus SAO shock increased the loss of the lysosomal protease cathepsin D from normal and ischemic myocardial tissue. Moreover, cats subjected to MI and given LE exhibited increased mortality and decreased clearance of infused lysosomal hydrolases. These results indicate that conditions affecting increased plasma levels of hydrolases promote increased disruption of normal and ischemic myocardial tissue. These findings are consistent with the concept that hydrolases originating in the splanchnic viscera during shock play a role in enhancing damage to normal and ischemic myocardial tissue following coronary artery occlusion.

LOSS of lysosomal enzymes has been shown to be an early consequence of myocardial ischemia.^{12,15,18} Ricciutti¹⁶ found a significant loss of acid phosphatase from canine papillary muscle as early as one hour following coronary artery occlusion in the dog. Recently, we demonstrated the loss of the lysosomal protease, cathepsin D, from the myocardium of cats within 5 hours of coronary artery occlusion.²⁰ Moreover, the decrease in

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cathepsin D activity correlated closely with the myocardial loss of creatine phosphokinase and the increase in S-T segment elevation 5 hours after coronary artery occlusion. These results indicate that myocardial lysosomal disruption is an early consequence of coronary artery occlusion, and that release of lysosomal proteases within the ischemic myocardium is associated with increased loss of myocardial cellular enzymes following coronary vascular occlusion. This phenomenon may be analogous to the release of lysosomal hydrolases from the ischemic splanchnic region during circulatory shock.

Since the plasma activities of lysosomal enzymes have been shown to markedly increase in a variety of types of circulatory shock,^{10,19} and because high circulating lysosomal hydrolase activities sensitize the myocardium to cardiodepressant factors,⁵ it would be of interest to determine whether extracardiac lysosomal hydrolases exacerbate the injury to the myocardium following coronary artery ligation. The present study, therefore, was designed to examine the effect of endogenous and exogenously administered splanchnic lysosomal enzymes upon the cellular integrity of normal and ischemic myocardial tissue after acute coronary artery occlusion.

Methods

Coronary Artery Occlusion

Male and female cats (2.0 - 3.5 kg) were anesthetized with sodium pentobarbital (30 mg/kg) given intravenously. The trachea was cannulated and positive pressure respiration was instituted with a Harvard small animal respirator. Catheters were placed within the right external jugular vein and left common carotid artery for the recording of central venous and mean arterial blood pres-

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tures, respectively. Pressures were recorded continuously using appropriate Statham P-23 pressure transducers coupled to a Beckman Type R Dynograph. Needle electrodes were placed subcutaneously to allow continuous recording of lead III of the electrocardiogram. A mid-sternal thoracotomy was performed, the heart exposed, the left coronary artery was cleared of surrounding tissue, and a 3-0 silk ligature was placed under the vessel. In cats subjected to acute myocardial ischemia, the ligature was tied tightly around the left coronary artery, 13–15 mm from the coronary ostium. Sham-operated cats were subjected to the surgical procedures and samplings equivalent to cats subjected to coronary artery occlusion except that the coronary artery was not ligated.

In additional groups of cats, an increased level of circulating lysosomal enzymes was achieved by the institution of splanchnic artery occlusion shock or by infusion of a large granule fraction of liver homogenate termed liver extract. Splanchnic arterial occlusion shock was produced by occlusion of the celiac, superior and inferior mesenteric arteries two hours after coronary artery ligation or at an equivalent time in sham-operated cats. The splanchnic artery occlusion was maintained for two hours followed by release of the splanchnic arterial clamps. The animals were observed for one hour after release or until the blood pressure declined to a value of 35 mm Hg for 20 minutes. A similar time course was observed with cats given liver extract. The extract was infused into the jugular vein catheter over a period of 10 minutes beginning two hours after myocardial ischemia, or at an equivalent time in sham-operated cats. The cats were then observed for 3 hours or until arterial blood pressure stabilized at a value of 35 mm Hg or less for 20 minutes.

Cats were randomly placed into one of the following experimental groups: 1) sham operation (sham MI), 2) myocardial ischemia for 5 hours after occlusion of the left coronary artery (MI), 3) sham myocardial ischemia and splanchnic artery occlusion shock (sham MI + SAO), 4) myocardial ischemia and splanchnic artery occlusion shock (MI + SAO), 5) sham myocardial ischemia and infusion of liver extract (sham MI + LE), and 6) myocardial ischemia and infusion of liver extract (MI + LE).

Preparation of Lysosomal Liver Extract (LE)

An extract of cat liver rich in lysosomal enzymes was prepared using a modification of the method described by Glenn *et al.*⁵ Approximately 30 grams of liver was placed in cold 0.375 M sucrose (1:5, w:v) and homogenized for 5 minutes using a Potter-Elvehjem homogenizer. The homogenate was centrifuged at 4 C at $1,000 \times g$ for 10 minutes and the sedimentable cell debris discarded. The supernatant was then recentrifuged at $12,500 \times g$ for 60

minutes. After centrifugation, the supernatant was discarded and the lysosomal pellet resuspended in distilled water. Krebs-Henseleit solution (i.e., compensating for the distilled water) was added and the volume adjusted to $\frac{1}{8}$ th of the original homogenization volume. The resultant preparation was warmed at 37 C prior to use. Cats were infused intravenously with 3.2 ml/kg of liver extract.

Sampling and Homogenization of Cardiac Tissue

Samples of arterial blood (4 ml) were withdrawn from the carotid catheter hourly in all cats. An additional blood sample was taken from cats immediately following infusion of the extract. Blood loss from sampling was replaced by an equal volume of Krebs-Henseleit solution warmed to 37 C. Blood was collected in polyethylene tubes containing two drops of sodium heparin, 1,000 units/ml (Upjohn, beef lung) and kept at 4 C until centrifugation. Blood was centrifuged at $2,400 \times g$ and 4 C for 15 minutes. The plasma was decanted and treated as described below. At five hours, the hearts were excised, rinsed in 0.9% NaCl solution at 4 C, rapidly weighed and placed in cold 0.25 M sucrose solution. The left ventricle was divided into ischemic and non-ischemic portions by inspection. Tissue supplied by arterial branches distal to the ligature appeared as cyanotic areas having patchy subendocardial hemorrhagic regions.

Ischemic or non-ischemic tissue was homogenized in 0.25 M sucrose (1:10, w:v) containing 1 mM ethylenediaminetetraacetic acid and 0.1 mM mercaptoethanol for the determination of myocardial creatine phosphokinase activity.¹⁷ The tissue preparation for the creatine phosphokinase determinations were treated according to the method of Kjekshus and Sobel.⁸ Additional portions of ischemic or adjacent normal ventricular tissue were minced and homogenized in 0.25 M sucrose (1:10, w:v) for subsequent determination of lysosomal enzymes. Each sample of myocardium was homogenized twice for 15 seconds using a Virtis homogenizer at a speed setting of 9.0. The homogenates were centrifuged at $800 \times g$ for 10 minutes and the cell debris discarded. The supernatants were then centrifuged at $36,000 \times g$ for 30 minutes at 4 C. Supernatants were assayed for cathepsin D activities. Cardiac homogenates from sham-operated cats were derived from left ventricular tissue anatomically equivalent to the ischemic and normal areas present in ischemic hearts.

Biochemical determinations

Aliquots of the plasma, liver extracts, and supernatants of cardiac homogenates were analyzed for lysosomal hydrolase activity using cathepsin D as a marker. Cardiac and plasma cathepsin D activities were assayed using the method of Anson.¹ The protein concentration of plasma,

TABLE 1. S-T Segment Elevation During Acute Myocardial Ischemia

Experimental Group	Time (min)		
	0	30	300
Sham MI (4)	0.03 ± 0.03	0.03 ± 0.03	0.03 ± 0.03
MI (4)	0.07 ± 0.05	0.63 ± 0.03**	0.43 ± 0.05*
Sham MI + SAO (7)	0.09 ± 0.04	0.04 ± 0.03	0.07 ± 0.06
MI + SAO (8)	0.08 ± 0.03	0.67 ± 0.06**	0.51 ± 0.10**
Sham MI + LE (6)	0.05 ± 0.03	0.08 ± 0.05	0.15 ± 0.04†
MI + LE (7)	0.03 ± 0.02	0.63 ± 0.07**	0.04 ± 0.09*

All values are mean S-T segment elevations in millivolts ± SEM. LE = liver extract, MI = myocardial ischemia, SAO = Splanchnic occlusion shock.

*P < 0.01 from 0 time †P < 0.05

**P < 0.001 from 0 time

liver extracts, and supernatants of cardiac tissue was determined using the biuret method.⁶ Cathepsin D activity is expressed as milliequivalents of tyrosine × 10⁻⁴ released from bovine hemoglobin/mg protein per hour at 37 C. Creatine phosphokinase activities of plasma and supernatants of cardiac homogenates were determined according to the method of Rosalki.¹⁷

Results

The initial values of mean arterial blood pressure and heart rate were similar in sham-operated cats and in cats subjected to myocardial ischemia alone. Ligation of the left coronary artery produced a marked increase in S-T segment elevation after 30 minutes (Table 1). A significant S-T segment elevation persisted for the 5 hour duration of the experiment.

In addition to the increased S-T segment elevation, plasma CPK activity increased markedly in cats subjected to coronary artery ligation. Fig. 1 shows the increase in plasma CPK activity in the 6 experimental groups. In each case, myocardial ischemia produced a significantly greater increase in CPK activity than that found for the respective sham-operated animals after 5 hours. Furthermore, the plasma appearance of endogenous or exogenously administered lysosomal enzymes following splanchnic arterial occlusion shock or infusion of liver extract, respectively, did not significantly modify the increase in CPK activity observed in cats subjected to acute myocardial ischemia. However, sham-operated cats subjected to SAO shock exhibited a significantly greater increase in plasma CPK activity than did cats subjected to only the sham operation. Fig. 2 summarizes

the net relative specific activity in plasma of the lysosomal protease cathepsin D comparing each group of MI cats to the appropriate sham-operated control group. Plasma cathepsin D activities are shown just prior to ligation of the left coronary artery and at hourly intervals for 5 hours. There was no significant difference between the plasma cathepsin D activities in MI cats and the activities found in sham MI cats at anytime during the 5 hour experimental period. Similarly, there was no significant difference in the plasma cathepsin D activity of SAO cats until after release of the splanchnic artery occlusion. Following release, there was a significant increase in the plasma cathepsin D activity of cats subjected to MI plus SAO shock as compared to sham-operated cats of this group.

The greatest increase in plasma cathepsin D activity occurred following infusion of liver extract. Despite the fact that both groups of cats given liver extract received comparable amounts of exogenous lysosomal enzymes (i.e., 48 vs 49 cathepsin D units/mg protein), the cathepsin D activity in the plasma of the sham-operated cats was 3.6 ± 0.6 units/mg protein compared with 5.6 ± 0.3 units/mg protein (mean ± standard error of the mean) in cats with ischemic myocardium just after completion of the liver extract infusion. This significantly greater circulating level of cathepsin D in cats subjected to myocardial ischemia and given liver extract (Fig. 2) persisted for at least two hours. Moreover, 4 of the 7 cats subjected to the combination of myocardial ischemia plus liver extract died prior to the end of the 5 hour experi-

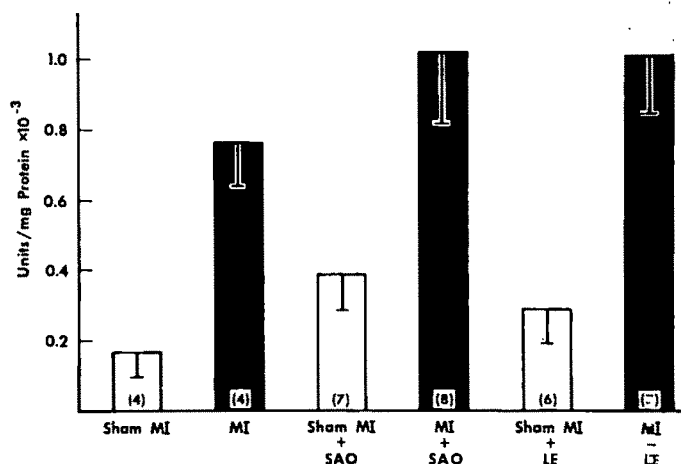


FIG. 1. Increase in plasma CPK activity (initial sample minus final sample) after 5 hours. Values are means ± SEM for the number of cats shown in parentheses. Comparable increases in plasma CPK activity were found in sham MI and sham MI + LE cats. Sham MI + SAO cats had a greater increase in plasma CPK activity than did sham MI cats. MI cats, whether combined with SAO or LE, exhibited similar marked increases in plasma CPK activity after 5 hours. (P < 0.01 for Sham vs. MI, Sham MI + SAO vs. MI + SAO and for Sham MI + LE.) Units, see text. CPK = creatine phosphokinase, LE = liver extract, MI = myocardial ischemia, SAO = splanchnic artery occlusion.

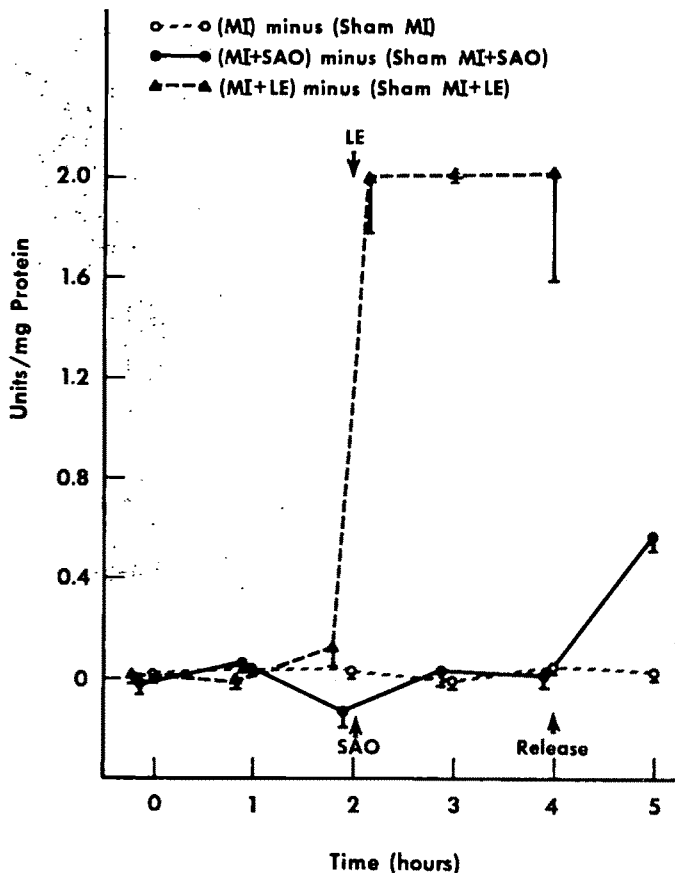


FIG. 2. Net plasma cathepsin D Activity in MI cats, MI + SAO cats, and in MI + LE cats. Values are means $\pm$ SEM of the difference between the plasma level found in MI cats minus the plasma cathepsin D found in the appropriate sham-operated cat at every point. None of the values are significantly different over the first two hours. The arrow labelled LE indicates the beginning of infusion just after the 2 hour sampling in these cats. The lower arrows indicate occlusion of celiac, superior and inferior mesenteric arteries just after the 2 hour sampling (SAO) and release of the occlusive clamps just after the 4 hour sampling. The 5 hour net value is higher than MI series in the SAO series ($P < 0.01$) and LE series ($P < 0.001$). LE = liver extract, MI = myocardial ischemia, SAO = splanchnic artery occlusion.

mental period. Thus, the cats not surviving 5 hours had a plasma cathepsin D activity of 4.3 ± 0.8 units/mg protein (mean $\pm$ SEM) at 4 hours, while the 3 surviving cats in the same group had a plasma cathepsin D activity of 2.5 ± 0.6 units/mg protein after 4 hours ($P < 0.02$). Furthermore, those cats which survived the full 5 hours after infusion (5 of 6 sham-operated and 3 of 7 myocardial ischemic cats) exhibited similar plasma cathepsin D activities at that time, whether or not the cats had undergone coronary artery ligation. Thus, after 5 hours sham-operated cats and MI cats had plasma cathepsin D activities of 1.0 ± 0.2 and 1.2 ± 0.2 units/mg protein, respectively. These data indicate that non-surviving MI cats receiving liver extract experienced a phase of reduced clearance of cathepsin D activity. The half-time for the clearance of cathepsin D from the plasma of MI + LE

cats was 158 minutes compared with 73 minutes in sham MI + LE cats.

In order to assess the effect of lysosomal hydrolases or myocardial ischemia upon the cellular integrity of the myocardium, myocardial CPK and cathepsin D specific activities were determined. Fig. 3 illustrates the CPK specific activity present in normal and ischemic myocardial tissue of all groups of cats. Sham-operated animals showed similar creatine phosphokinase activities in tissue equivalent to the normal and ischemic left ventricular tissue of ligated cats (i.e., about 60 units/mg protein). However, the ischemic myocardial area in cats subjected to coronary artery ligation showed a 36% decrease in creatine phosphokinase activity compared to adjacent normal tissue. Furthermore, in sham-operated cats subjected to splanchnic arterial occlusion shock or infusion of liver extract, both areas of myocardial tissue showed a 17% reduction ($P < 0.02$) in CPK activity compared to non-ischemic myocardial tissue of cats subjected to either the sham MI or MI alone. In fact, the ischemic tissue in all myocardial ischemic groups showed a significant reduction in CPK activity when compared to the normal tissue in those hearts.

Determinations of changes in myocardial cathepsin D activity revealed a pattern similar to that found for CPK activity in the different experimental groups. In all sham-operated animals, the cathepsin D specific activities of normal and presumed ischemic tissue were similar. Moreover, myocardial ischemia resulted in a reduction of 34% in the cathepsin D activity of ischemic myocardium. Reductions of 25% of the cathepsin D activ-

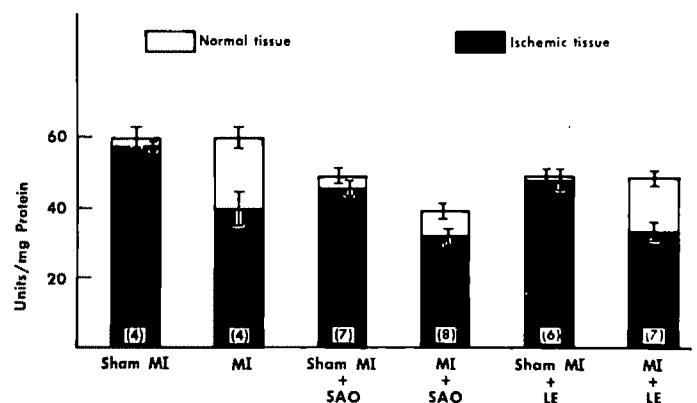


FIG. 3. Myocardial CPK activities in normal and ischemic myocardium. Values are means $\pm$ SEM for the number of hearts shown in parentheses. Each ventricle was divided into normal and ischemic areas. Thus, in sham-operated cats, tissue indicated as ischemic was excised from the area that would have been the ischemic area in MI cats. Activity in normal tissue is significantly lower ($P < 0.02$) than sham MI in all other groups except the MI group. Ischemic tissue is significantly lower than the equivalent area in sham MI cats in MI, MI + SAO and MI + LE cats ($P < 0.01$) as well as in sham MI + LE cats ($P < 0.02$). CPK = creatine phosphokinase, LE = liver extract, SAO = splanchnic artery occlusion.

ity were found in the ischemic tissue of cats subjected to MI and either SAO shock or infusion of LE.

Discussion

Ligation of the left coronary artery in cats resulted in marked elevations of the S-T segment of the electrocardiogram recorded 30 minutes after coronary artery occlusion. In contrast, sham-operated cats did not exhibit significant S-T segment elevations at this time. Prior to induction of splanchnic arterial occlusion shock or infusion of liver extract, all cats subjected to acute myocardial ischemia exhibited similar S-T segment elevations. Moreover, at 5 hours, all groups subjected to myocardial ischemia exhibited maintained S-T segment elevations (Table 1). Therefore, neither SAO shock nor infusion of LE altered the elevated S-T segment of the electrocardiogram which was maintained throughout the experimental period. However, there was an enhanced S-T segment elevation after 5 hours in sham MI cats given LE. These results suggest that LE alone may induce myocardial damage reflected in the electrocardiogram; however, these electrocardiographic changes are usually masked by the greater insult of coronary artery occlusion.

Myocardial ischemia alone did not increase plasma cathepsin D activity above that found in the sham-operated cats. These results are in agreement with those of a previous study,²⁰ which indicated that in the absence of circulatory shock, plasma activities of cathepsin D do not significantly increase. In this study, cats subjected to myocardial ischemia alone maintained sufficient levels of mean arterial blood pressure 5 hours after coronary artery occlusion to prevent endogenous release of lysosomal hydrolases. This was also the case in the extrasplanchnic region in SAO shock cats prior to release of the splanchnic vascular clamps. In this regard, at the end of 4 hours of experimentation, mean arterial blood pressure and plasma cathepsin D activity of cats subjected to coronary artery ligation or combined ligation and splanchnic arterial occlusion were very similar. However, release of the occlusive clamps resulted in a two-fold increase in the plasma cathepsin D activity of cats in MI + SAO cats compared to sham MI + SAO cats. This occurred despite the fact that the mean arterial blood pressure were at indistinguishable levels of circulatory shock one hour after release of the splanchnic artery clamps. These results suggest that the increased cathepsin D activities found after 5 hours in cats subjected to SAO shock and coronary artery ligation are either 1) of cardiac origin, or 2) that the combination of interventions enhanced the release or impaired the clearance of lysosomal enzymes independent of mean arterial blood pressure. It is doubtful that these enzymes originated in the heart, since the total content within the heart is not large. Moreover, Hill et al.⁷ have shown that within 45 minutes

of coronary artery ligation, blood flow to the splanchnic organs is markedly diminished. Thus, the initial one hour period of myocardial ischemia may result in splanchnic ischemia, a condition which enhances the release of lysosomal enzymes following splanchnic artery occlusion and release.

Particularly striking is the difference between circulating cathepsin D activities of cats subjected to myocardial ischemia and given liver extract compared with their sham-operated controls. Despite the fact that similar enzyme activities were injected into both groups of cats, the level of cathepsin D remained high in MI + LE cats as compared to sham MI + LE cats. Indeed, the half-time for the clearance of cathepsin D activity from the plasma was 158 minutes in the former versus 73 minutes in the latter. The half-time of cathepsin D in the plasma of sham MI + LE cats was similar to that reported by Fr  dlund et al.² in pigs for intravenously infused β -glucuronidase, another lysosomal acid hydrolase. These authors also found that intravenous infusion of acid hydrolases was without lasting effect in an otherwise normal animal. Apparently, in the absence of any further insult, such as myocardial ischemia, the plasma clearance of infused hydrolases may be rapid enough to prevent severe tissue injury. However, the combination of myocardial ischemia and liver extract proved to be deleterious. Thus, the greater cathepsin D activity in MI + LE cats, was associated with increased mortality.

Both the circulating plasma protease activities and the degree of plasma proteolysis markedly increase in SAO shock³ and in hemorrhagic shock.¹⁹ Increased proteolysis in the plasma of animals and man in circulatory shock^{10,11} suggest that increased circulating levels of lysosomal proteases might promote damage to myocardial tissue. Our findings indicate that such damage occurs in cats subjected to increased circulating levels of lysosomal enzymes (Fig. 3). Five hours after coronary artery occlusion, myocardial CPK activity was reduced 36% in ischemic myocardial tissue, a decrease which is in agreement with our previous findings in the cat²⁰ and with those of Kjekshus and Sobel⁸ in the rabbit and Maroko et al.¹³ in the dog. However, the finding that the CPK activity of non-ischemic myocardium is reduced following SAO shock or infusion of LE is a new finding. These results suggest that increased activities of circulating lysosomal enzymes promote loss of myocardial enzymes from non-ischemic tissue. Moreover, the added insult of myocardial ischemia in combination with splanchnic arterial occlusion shock resulted in a further loss of CPK activity from both the normal and ischemic myocardium. However, the combination of MI with LE did not enhance CPK loss from normal tissue despite the fact that the CPK loss from ischemic tissue was enhanced in these cats. The reason for this differential response is not clear at present.

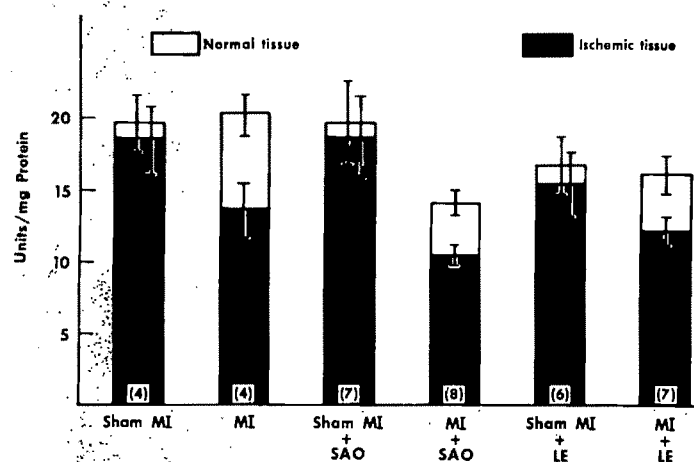


FIG. 4. Myocardial cathepsin D activity in normal and ischemic myocardium. Values are means $\pm$ SEM for the number of hearts shown in parentheses. Activity in normal tissue is significantly lower than that in sham MI group only in the MI + SAO ($P < 0.02$) and in the MI + LE ($P < 0.05$) group. Enzyme activity in ischemic tissue was significantly lower than normal tissue in the MI group ($P < 0.01$), MI + SAO and MI + LE groups ($P < 0.02$). LE = liver extract, MI = myocardial ischemia, SAO = splanchnic artery occlusion.

Glenn and Lefer⁴ reported that the loss of myocardial cathepsin D activity was insignificant following the development of hemorrhagic shock in dogs. Our results in sham-operated cats are in agreement with this finding (Fig. 4). This may be a reflection of the capacity of the coronary circulation to autoregulate its blood flow under a variety of adverse conditions. However, during coronary artery occlusion, when the ischemia of the myocardium is directly produced, myocardial lysosomal hydrolase activities are reduced indicating a loss of activity from the heart under these conditions.^{14,16} In the present study, the combination of MI + SAO shock apparently enhanced the loss of cathepsin D activity from normal, non-ischemic tissue and from ischemic tissue within the heart. This would also suggest that SAO, while not directly affecting loss of myocardial cathepsin D, in some ways promotes injury of non-ischemic tissue following induction of myocardial ischemia.

We recognize that neither SAO shock, nor LE infusion results in a selective addition of pure lysosomal hydrolases to the circulation. Therefore, factors other than acid hydrolases may be contributing either directly or indirectly to the myocardial cellular damage observed in this study. A variety of vasoactive and enzymatic substances could contribute to this process, and potentiate the deleterious effect of the lysosomal hydrolases. However, our results are consistent with the hypothesis that substances of splanchnic origin including lysosomal hydrolases are released in conditions of circulatory shock and disrupt the cellular integrity of normal and ischemic myocardial tissue.

Acknowledgments

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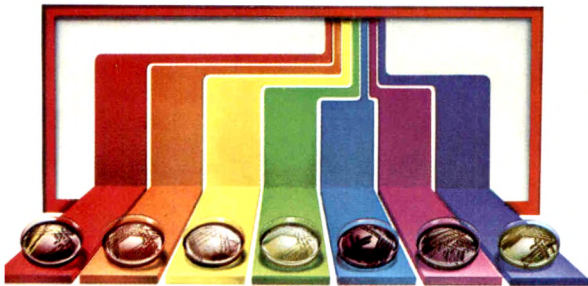
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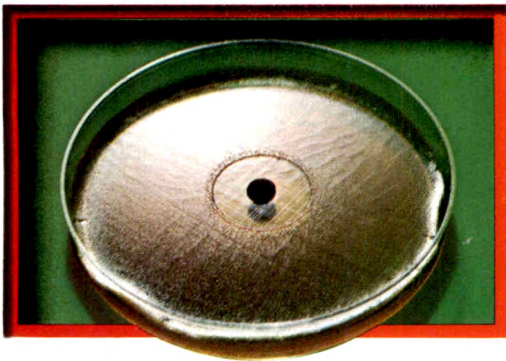


In serious gram-negative infections*

Three good reasons to initiate therapy with **Garamycin[®] Injectable** (gentamicin sulfate)



1. Unique spectrum.



**2. Incidence of bacterial
resistance is low and has
not increased significantly.**



**3. Relatively low order of
adverse renal and eighth
nerve reactions when used
as directed.**

*Due to susceptible organisms

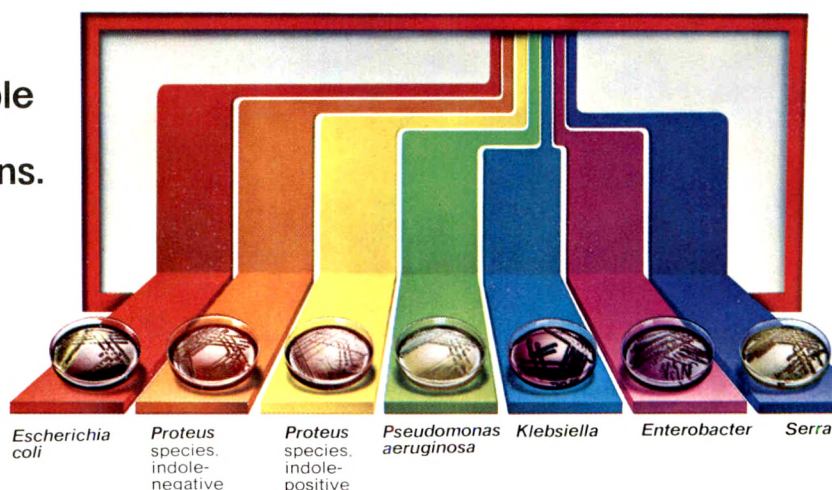
1. Unique spectrum.

Garamycin Injectable (gentamicin sulfate) is active against susceptible strains of seven major gram-negative pathogens.

These are:

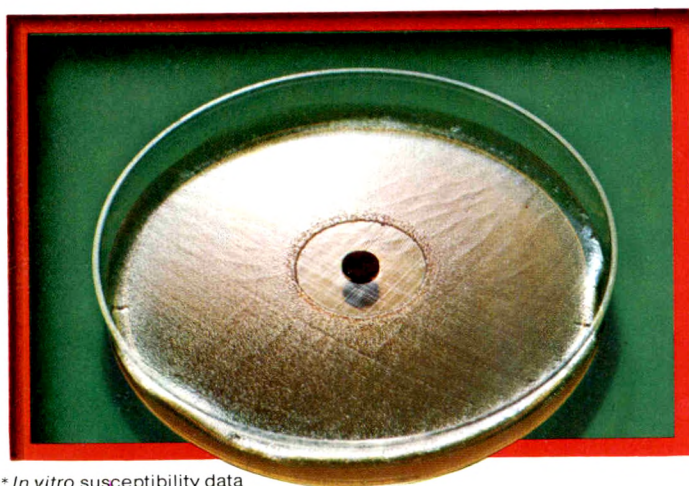
Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella
Enterobacter } species
Serratia

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*In vitro** susceptibility virtually unchanged



* *In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.

In a five-year study¹ in over 100 hospitals, gram-negative pathogens identified and tested demonstrated high susceptibility to GARAMYCIN. From 1970 through 1974, there was virtually no change in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

In the seven or eight years' experience of one investigator² where gentamicin has been restricted to parenteral use, resistance has not appreciably changed.

Resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported.

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3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

Adverse renal reactions

The risk of adverse renal reactions is low in patients with normal renal function. Usually manifested by nitrogen retention as evidenced by a rising BUN and creatinine, they occur most often in patients with pre-existing renal damage and in patients receiving larger than recommended doses or treated for longer periods of time than recommended. See Warning Box below.



Adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions with GARAMYCIN Injectable is relatively low. When occurring, the effect is predominantly on the vestibular branch of the eighth cranial nerve, resulting in vestibular dysfunction with vertigo and tinnitus. These symptoms have, in many cases, been transitory. The known effect on the auditory branch to date mostly has involved only the high-frequency hearing ranges. See Warning Box below.



A logical choice in serious gram-negative infections[†]

pneumonia
urinary tract infections
septicemia
wound infections

[†] Due to susceptible organisms

Garamycin[®]
gentamicin sulfate injectable
40mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

See Clinical Considerations section which follows...

A logical choice in serious gram-negative infections*



GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin
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WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, *Proteus* species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given

intramuscularly or intravenously.

For Intramuscular Administration:

Patients with normal renal function*

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lbs) the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. If dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

*In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burn or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

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AHFS Category 8:12

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Garamycin®

gentamicin sulfate injectable

40mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

*Due to susceptible organisms

Quantitative Bacterial Analysis of Comparative Wound Irrigations

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It is a biologic fact that all open wounds contain bacteria and remain contaminated with varying levels of bacteria until successful wound closure has been accomplished. The sine qua non in the management of the contaminated wound has been and remains adequate sharp debridement. In a standardized experimental model, three methods of irrigation were compared employing quantitative bacteriology of tissue to evaluate their effectiveness at decreasing bacterial levels and reducing wound infection. The pulsating jet lavage was found to be significantly better than gravity flow irrigation or wound irrigation with a bulb syringe. These data on tissue biopsies support previous reports using surface and wound exudate cultures.

TRAUMATIC wounds, whether produced in military or civilian surroundings, are uniformly contaminated.^{1,16} In addition to the large inoculum of bacteria, these wounds are often complicated by debris, blood clot, and necrotic tissue. Proper mechanical debridement and delayed closure of contaminated wounds have markedly reduced the incidence of infection.^{5,14,19} The value of irrigation as an adjunct to mechanical debridement is less clear. Singleton, et al.²⁰ and Peterson¹⁵ have shown that saline irrigation decreases the incidence of wound infection and that the decrease was proportional to the amount of irrigating solution used. Conversely, several investigators have reported that low pressure saline irrigation is ineffective in preventing wound infections.^{6,7,12}

Recently a great deal of data has emerged suggesting that a pulsating irrigation stream delivered at high pressure and with a high flow effectively decreases bacteria, foreign bodies, and necrotic crushed tissue in wounds and decreases the incidence of resultant wound infection.^{3,4,7,10} These data have been based on a semi-quantitative technique of smear cultures obtained from the surface of wounds or from pyogenic exudates from the wounds. Multiple studies over the past 10 years have

shown that infection rates are best correlated with the tissue level of bacteria and that surface cultures or cultures of wound discharges are often misleading.¹⁹

The present study was undertaken to evaluate the effectiveness of various types of wound irrigation techniques in decreasing the tissue bacterial level in experimental wounds.

Materials and Methods

One hundred male Sprague-Dawley rats weighing 200 to 250 grams were divided in two major groups. The animals were individually caged and given unrestricted amounts of food and water. The animals were anesthetized with intraperitoneal pentobarbital sodium (30 mg/kg). Skin preparation consisted of clipping the hair from the back of each animal followed by skin cleansing with Betadine® solution.* The experimental model consisted of a standard incision 4 cm in length and 5 mm lateral and parallel to the vertebral column. The incision was carried through the skin, panniculus carnea, and 4 mm into the paraspinal muscles. When necessary, hemostasis was accomplished by sterile gauze pressure.

Group I—Wounds Contaminated with Bacteria Only

The wounds in the first major group were topically inoculated with 5×10^7 *Staphylococcus aureus* organisms and 5×10^7 *Escherichia coli* organisms from fresh 18 hour broth cultures. After a 30 minute contamination period, the animals were divided into four sub-groups and tissue biopsies taken for quantitative and qualitative bacterial analyses.^{13,17} The sub-groups were treated in one of the following ways.

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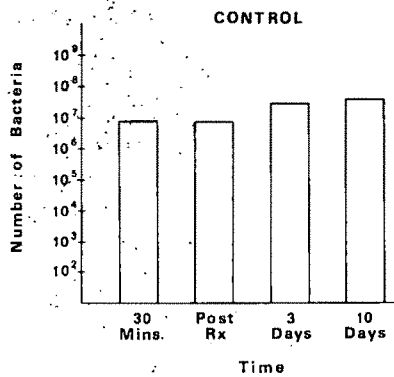


FIG. 1. Graph of geometric means of animals in control sub-group inoculated with bacteria alone showing persistently high bacterial counts throughout experimental period.

A. Control. The wounds in the control sub-group underwent closure with interrupted monofilament nylon sutures.

B. Gravity flow irrigation. The wounds in the gravity flow sub-group were irrigated with 300 ml of normal saline from a standard intravenous bottle and tubing with the bottle being suspended at a constant height 60-65 cm above the wound. The tip of the intravenous tubing was held 2 to 3 cm from the wound. Following irrigation a second tissue biopsy was obtained and the wounds closed.

C. Bulb syringe irrigation. The wounds in the bulb syringe sub-group were irrigated with 300 ml of normal saline using a conventional 50 ml Dakin's syringe. The bulb was squeezed firmly and rapidly and moved back and forth over the wound with the tip 4 to 5 cm above the wound. Following irrigation a repeat biopsy was obtained and the wounds closed.

D. Pulsating jet lavage. Wounds in the pulsating jet lavage sub-group underwent irrigation with 300 ml of normal saline delivered in a pulsating stream through a four hole tip at 50 pounds psi (approximately three grams of pressure per square millimeter of surface) over a period of 20 seconds. The tip was held 4 to 5 cm from the wound surface. The device used for this purpose pulsates at 1200 cycles per minute, delivering 800 to 1000 ml per minute at a variable pressure of 2 to 75 psi using a four-hole tip. Immediately following lavage, a second biopsy was taken and the wounds closed.

Three days after wounding, each of the wounds was inspected for gross infection and was opened under aseptic conditions. Tissue biopsies were again obtained for quantitative and qualitative bacterial analyses. The wounds were reclosed with monofilament nylon sutures. At ten days, the surviving animals were sacrificed, their wounds grossly inspected, and tissue cultures performed.

Group II—Wounds Contaminated with Bacteria and Foreign Body

Because bacteria is rarely present alone in clinically contaminated wounds, the second major group of ani-

mals was contaminated with bacteria and a foreign body. In addition to 5×10^7 *Staphylococcus aureus* and 5×10^7 *Escherichia coli* organisms, Group II animals had 0.5 grams of sterile sand introduced into their wounds. After a 30 minute contamination period, repeat bacterial analyses were performed and the animals divided into four sub-groups and treated as before: A. Control, B. Gravity flow irrigation, C. Bulb syringe irrigation, D. Pulsating jet lavage. Each of the animals in these sub-groups was treated as described in Group I with the exception of the addition of sand as a foreign body in their wounds.

Results

Group I—Wounds Contaminated with Bacteria Only

A. Control. The results for the control sub-group are diagrammed in Fig. 1 which shows the geometric means of the bacterial counts of the animals. The control animals obviously had no treatment and, therefore, the bacterial count listed in the post-treatment column is the same as in the pre-treatment biopsy. However, the bacterial counts increased over the initial pre-treatment level at 3 and 10 days, from 8×10^6 organisms per gram of tissue to 3×10^7 and 4×10^7 organisms per gram of tissue respectively. All wounds were grossly infected.

B. Gravity flow irrigation. Gravity flow was ineffective in lowering the bacterial counts after treatment and also allowed an increased bacterial growth above the pre-treatment levels of 1×10^6 organisms per gram of tissue to 4×10^7 organisms per gram of tissue at three days (Fig. 2). Approximately 85% of these wounds were grossly infected.

C. Bulb syringe irrigation. The bulb syringe did lower the bacterial count to 9×10^5 organisms per gram of tissue from a pre-treatment level of 6×10^6 organisms per gram

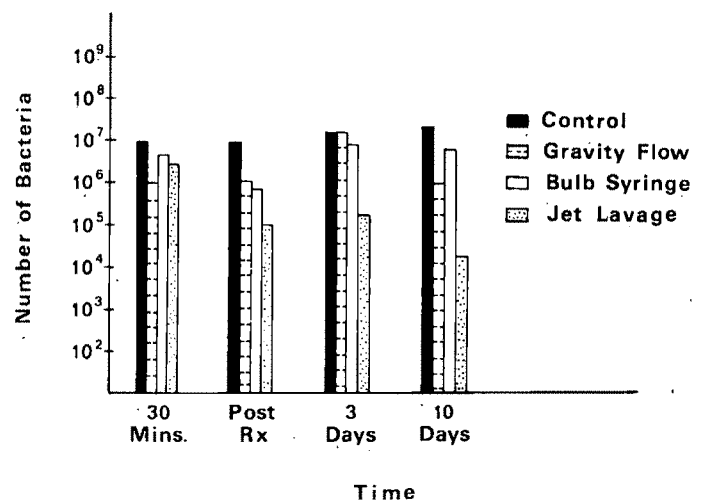


FIG. 2. Comparative wound irrigation in Group I animals whose wounds were contaminated with 5×10^7 *Staphylococcus aureus* organisms and 5×10^7 *Escherichia coli* organisms.

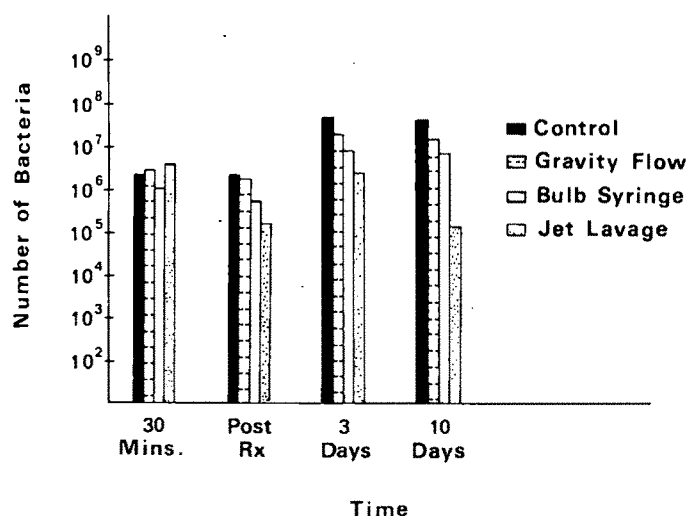


FIG. 3. Comparative wound irrigation in Group II animals whose wounds were contaminated with bacteria and foreign body.

of tissue. This decrease was statistically significant ($P < 0.01$). However, it did not prevent a rebound effect at 3 and 10 days (Fig. 2). Although 85% of these wounds were grossly infected at 3 days, the number had decreased to 60% at 10 days.

D. Pulsating jet lavage. The pulsating jet lavage significantly decreased the bacterial count from 4×10^6 to 1×10^5 ($P < 0.01$). It was the only technique which kept the bacterial count below pre-treatment levels throughout the experiment (Fig. 2). At 3 days and at 10 days the pulsating jet lavage was not only significantly better than the control sub-group but also significantly better than the bulb syringe sub-group. At 10 days the control wounds had bacterial counts of 4×10^7 organisms per gram of tissue, while the bulb syringe and pulsating jet lavage wounds had 9×10^6 and 3×10^4 organisms per gram of tissue respectively. Only 20% of the wounds were grossly infected.

Summarizing the Group I animals, the bulb syringe and the pulsating jet lavage significantly decreased the bacterial counts immediately after treatment. At 3 days only the pulsating jet lavage was significantly better than the control and it was also significantly better than the bulb syringe. At ten days, again only the lavage was better than the control and also better than the bulb syringe. Only the pulsating jet lavage consistently lowered the bacterial count to 10^5 or fewer bacteria per gram of tissue, and this resulted in significantly fewer infections.

Group II—Wounds Contaminated with Bacteria and Foreign Body

A. Control. Wounds in the control sub-group had bacterial counts whose geometric means increased from 4×10^6 in the pre-treatment stage to 9×10^7 organisms per

gram of tissue at 3 days and 6×10^7 organisms per gram of tissue at 10 days (Fig. 3). All wounds were grossly infected at 3 and 10 days.

B. Gravity flow irrigation. The gravity flow irrigation was again ineffective in decreasing the bacterial count. The post-treatment count of 3×10^6 organisms per gram of tissue was not significantly different from the pre-treatment level of 6×10^6 (Fig. 3). All wounds became grossly infected.

C. Bulb syringe irrigation. As compared to the Group I animals without the foreign body addition, the bulb syringe irrigation did not significantly reduce the bacterial count in the animals in Group II and by 10 days all of these wounds became infected. The pre-treatment levels of 1×10^6 organisms per gram of tissue were only lowered to 7×10^5 organisms per gram of tissue and by 3 days the counts had increased to 1×10^7 (Fig. 3).

D. Pulsating jet lavage. Only the pulsating jet lavage decreased the bacterial count by a significant amount ($P < 0.01$). The post-treatment level was 3×10^5 organisms per gram of tissue compared to a pre-treatment level of 6×10^6 organisms per gram of tissue (Fig. 4). Although at 3 and 10 days the bacterial counts hovered around 10^5 organisms per gram of tissue, only 50% of the wounds were grossly infected at 10 days.

To summarize the group of animals contaminated with both bacteria and foreign body, only the pulsating jet lavage significantly reduced the bacterial count in the post-treatment period. By 3 days, and again at 10 days, this significance was much less, being only at the 95% confidence level.

Discussion

In any traumatic wound the ability of the host to combat infection is greatly influenced by the level of bacteria, foreign body contamination, necrotic tissue, and blood clots.^{2,5,11,14} All surgical therapy must be directed toward rendering the local wound environment and the bacterial flora suitable for closure. Meticulous mechanical surgical removal of debris and contused or compromised tissue remains the single most important step in managing the

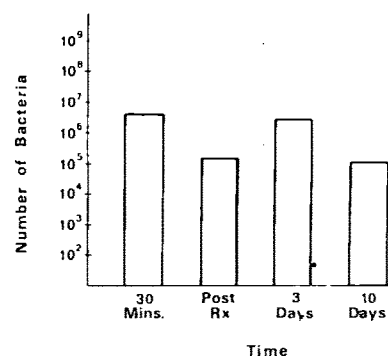


FIG. 4. Effect of the pulsating jet lavage on the tissue bacterial level in wounds contaminated with high levels of bacteria and foreign body.

contaminated wound. Irrigation may be an adjunct to debridement. Edlich, et al.⁶ Hopson, et al.¹² and Gross, et al.⁷ have demonstrated that the standard low pressure saline irrigation is ineffective at significantly reducing wound infections. Bhaskar and various of his associates in a series of publications have reported the use of a pulsating jet lavage operating at 70 pounds psi, and found it 7 times more effective than the bulb syringe in reducing infection rates;⁷ 3 to 7 times more effective in removal of foreign contaminants;^{4,9} and 40 times more effective in the removal of tissue fragments from crush wounds.^{8,10}

All studies previously reported employing the pulsating jet lavage were performed using semi-quantitative techniques. Bacterial studies were performed on surface swabs and wound exudates. As shown by Robson and Heggors,¹⁸ there is little correlation between the number and species of bacteria found in wound exudates and those reaching tissue levels. Wound infection is correlated with a bacterial count in tissue of greater than 10^5 bacteria per gram of tissue.^{13,17,19} Therefore, a comparison of irrigating techniques was performed to see which, if any, techniques available decreased bacterial counts to 10^5 or fewer bacteria per gram of tissue and thus resulted in fewer wound infections.

The fact that the gravity flow irrigation was ineffective at lowering the bacterial counts was not surprising. Previous authors have reported failure of low pressure irrigations.^{6,12} The bulb syringe did remove a great deal of bacteria, but was less effective than the pulsating jet lavage. This difference was even more marked when foreign body was added to the wound contamination. It is thought that the advantage of the pulsating jet lavage is its ability to deliver a pulsating stream producing rapid compression of the tissue and an interpulse decompression phase which allows the soft tissue with its inherent elasticity to rebound thus loosening the contamination particles. Also, once the particles are dislodged from the tissue the high flow rate of 800 to 1000 ml per minute removes them from the wound. The pulsating jet lavage was the only one of the 3 irrigating methods evaluated in this study which reduced the

bacterial level to the critical level of 10^5 or fewer bacteria per gram of tissue.

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Energy Metabolism of Experimental Wounds at Various Oxygen Environments

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Energy metabolism of healing tissue was studied in experimental wounds of rats chronically breathing 11% O₂, air or 55% O₂. Increasing oxygen supply elevated both P_o and P_{co} in the wound tissue. At the early phases of healing hypoxic wounds contained less DNA than normoxic or hyperoxic tissues. In hypoxia the accumulation of wound collagen was clearly retarded. Furthermore, tissue taken from wounds healing in hypoxic environments and tested *ex vivo* in air showed decreased capacity for glucose utilization, lactate production and oxygen consumption. Concentrations of AMP, ADP and ATP in repair tissue increased as healing progressed. The more oxygen available the higher the amounts of ADP and ATP. The AMP content was not affected by changes in local oxygen tension. These results support the earlier concept that the supply of oxygen in healing tissue may be rate-limiting. Reduction of available oxygen either by systemic hypoxia or by increased diffusion distance impedes healing.

AN ADEQUATE SUPPLY of oxygen is of vital importance for healing wounds since fibroblasts require oxygen for their energy production and collagen cannot be synthesized in the absence of molecular oxygen.^{7,16} In dead space wounds the rate of collagen accumulation has been shown to be, over a wide range, directly proportional to the amount of oxygen delivered to the wound.^{8,12} The ratio RNA/DNA of wound cells is known to increase during chronic hyperoxia.¹² This suggests that fibroblasts can increase their synthetic apparatus if added oxygen is available.

Earlier work from this laboratory demonstrated that hyperoxia shifts the wound metabolism from anaerobic towards aerobic glycolysis and thereby activates the citric acid cycle.²¹ This work has now been continued by testing the effects of hypoxia and hyperoxia on the concentrations of adenosine phosphates in an experimental wound model, the thin cellulose sponge implant. Wound tissue gases were measured by means of a Silastic tonometer embedded in the implant. Oxygen-induced changes in the amounts of wound collagen were compared with corresponding earlier data

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obtained from wounds with a larger dead space.¹² Furthermore, tissues taken from wounds healing in various oxygen environments were tested *ex vivo* in air for the capacity for glucose utilization, lactate production, and oxygen consumption.

Methods

Viscose cellulose sponge (Kongfoss/Fabrikker, Bygdo, Oslo, Norway) was used as a matrix for the growth of granulation tissue.²² The sponge was cut into thin sheets measuring 2.5 mm by 14 mm by 20 mm and weighing about 35 mg. This type of an implant was used in most experiments. For studies of tissue gas tensions the same material was cut into sheets of 2.5 mm by 14 mm by 70 mm, and a loop of gas-permeable Silastic tube, 15 cm long, with an outside diameter of 1.5 mm and an inside diameter of 1.2 mm, was implanted into the sponge by means of a wide-bore needle leaving the tube ends outside the sponge. These tubes are made for shunt systems used in the treatment of hydrocephalus (Atrial Catheter-J, B-190, Extracorporeal Medical Specialties Inc., King of Prussia, Pennsylvania) and are available in sterile packings.

All sponges were sterilized by boiling for 30 min in physiological saline solution prior to implantation. A low dorsal midline incision, 3 cm long, was made in male Wistar rats weighing 170-190 g and two sponge sheets of the smaller size were implanted under the skin, one on each flank. Sponge sheets containing the Silastic tube were implanted (only one per animal) longitudinally in the dorsal midline. The skin wound was closed with silk sutures. Implantations were performed under ether anesthesia.

Altogether 150 rats were used. They were divided into three equal groups and housed in air-tight transparent Perspex containers, volume about 23 l, 8 to 10 rats in each container. The first group was exposed to 11% O₂, the second group to 55% O₂, and the control group to air.

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Gases were supplied to the containers at atmospheric pressure and the flow rates were adjusted to 5 l per minute. The 55% oxygen mixture was obtained by passing pure oxygen through a gas mixer (Puritan,[®] Puritan-Bennet Corporation, Kansas City, Missouri). The 11% oxygen mixture was obtained by passing nitrogen through a similar mixer. The gas concentrations inside the chambers were checked 3 times a week. The CO₂ level remained always below 0.5%. The temperature was about 23 C and the relative humidity varied between 70 and 85%. Drinking water and food pellets were supplied *ad lib*.

All the measurements in implants were performed on the 6th, 10th or 15th day after implantation. Determinations of oxygen and carbon dioxide tensions in the repair tissue were carried out by the method of Niinikoski and Hunt¹³ as modified by Kivisaari and Niinikoski.⁹ During the measurements the rats were lightly anesthetized with intraperitoneally injected Nembutal and received their breathing gas through a head tent. The ends of the Silastic tube were exposed through a 1 cm incision and the tube was filled with hypoxic saline solution (P_{O₂}, 0 to 8 mm Hg) for two minutes. During this period P_{O₂} and P_{CO₂} equilibrations of 95 and 85% were achieved between the saline and the granulation tissue surrounding the Silastic tonometer. After the 2 min period the equilibrated fluid was sampled into an Astrup glass capillary tube by filling the tonometer with another dose of hypoxic saline from a 1 ml syringe. The ends of the glass capillary were sealed with wax and the capillary was stored on crushed ice. After all samples were collected the ends of the capillaries were cut off and the tubes were mounted one at a time into a microsample injector (Radiometer, Copenhagen, Denmark). The fluid in the capillary was injected into a thermostated cuvette (37 C) containing either a Clark oxygen electrode or a Severinghaus carbon dioxide electrode. The electrodes were connected to a gas monitor (Radiometer, Type PHM 71, Copenhagen, Denmark).

Zero adjustment of the O₂ electrode was obtained with gaseous nitrogen and the calibration took place with aerated saline (P_{O₂} 150 mm Hg) using the capillary sampling technique. The CO₂ electrode was also calibrated by the capillary sampling technique using saline solutions of two known CO₂ tensions (26 and 63 mm Hg).

The measurements of tissue gas tensions were made under clean but not strictly sterile conditions. On the occasions that the same wound was tested more than once, the ends of the Silastic tube were reimplanted under the skin and the skin was reclosed between tests.

For the assay of DNA, collagen hydroxyproline and adenosine phosphates in repair tissue, the rats were sacrificed by a blow on the neck, the implants were dissected out and immersed immediately in liquid nitrogen. With this procedure the implants were frozen within one minute after the death of the animal. The implants were stored at -80 C for two hours and then homogenized in 7 ml of

ice-cold 0.5 M perchloric acid in an Ultra-Turrax TP 18/2 N homogenizer (Janke & Kunkel KG, Staufen, Germany). The homogenates were centrifuged at 15,000 G at 4 C for 30 min. Supernatants and sediments were separated and stored at -80 C for analyses.

The sediment was mixed with 10 ml of 0.5 M perchloric acid and heated at 90 C for 40 min. The mixture was centrifuged at 20,000 G at 4 C for 30 min. The amounts of DNA and collagen hydroxyproline in the implant were determined from the supernatant. DNA was determined by the diphenylamine reaction as described by Burton.⁴ Hydroxyproline was assayed by the method of Woessner²³ after hydrolysis in 6 M hydrochloric acid.

The supernatant obtained after the initial extraction with cold perchloric acid was used for determinations of adenosine phosphates. AMP, ADP and ATP were assayed by standard enzymatic methods (C.P. Boehringer & Soehne, GmbH, Germany; Biochemical Test Combination) using a Perkin-Elmer UV-VIS Spectrophotometer 139.^{1,2} The measurements were performed at the wavelength of 340 nm.

For determinations of glucose consumption and lactic acid production implants were dissected out and rinsed in physiological saline solution to remove blood. Each implant was minced with scissors into pieces not exceeding 0.4 mm in diameter and subsequently incubated in 5 ml of Krebs-Ringer-HEPES medium supplemented with glucose (22.4 mM)¹⁹ in a metabolic shaker (Compenstat, Gallenkamp & Co., London, England). The medium was in contact with air as the oxygen source. After a preincubation period of 30 min, 1 ml of the medium was removed for estimations of glucose and lactate.^{3,6} The flasks were then covered with laboratory film to prevent evaporation and after an incubation of 60 min another 1 ml aliquot was taken for the assay of glucose and lactate. The rest of the incubation mixture was used for the determination of DNA. Glucose consumption and lactate production were calculated per milligram of DNA from concentration differences between pre- and postincubation samples.

For measurements of oxygen consumption by the granulation tissue the implants were quickly removed from rats and immersed in ice-cold Krebs-Ringer-HEPES medium supplemented with glucose (22.4 mM). Each implant was divided in three equal pieces which were minced separately with scissors as described above. Oxygen consumption rates of samples, each consisting of one third of an implant, were then measured in a Biological Oxygen Monitor[®] (Model 53, Yellow Springs Instrument Co., Yellow Springs, Ohio). The monitor has a polarographic O₂ electrode that fits air-tight into a glass chamber, where the sample was placed in 5 ml of Krebs-Ringer-HEPES medium containing glucose. At 37 C and ambient barometric pressure (P_{O₂} 150 mm Hg) 1 ml of this medium contains 5.0 μl of oxygen. Oxygen consumption in the chamber was detected as a fall of P_{O₂} in the incubation medium and the slope was monitored by a recorder (Servogor, Goerz

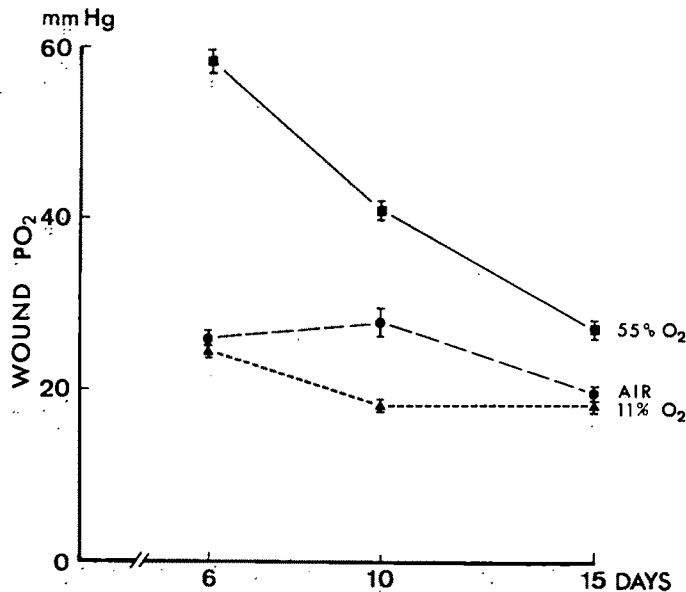


FIG. 1. Effect of changes in inspired oxygen tension on wound P_{O_2} . For 10-day values $P < 0.001$; analysis of variance. In Figs. 1 to 7 each value represents the mean $\pm$ the standard error of the mean of 4 to 8 animals.

Electro GmbH, Vienna, Austria). The decline in oxygen tension was linear from 150 to 100 mm Hg and observations of O_2 consumption rates were made at this area and calculated per milligram of DNA in the sample. DNA was determined from the incubation mixture after precipitation with ethanol.

Results

Figure 1 represents a summation of P_{O_2} measurements in implants of all ages. In general, the highest wound oxygen tensions were observed in rats breathing 55% O_2 and the lowest tensions in rats breathing 11% O_2 . However, on days 6 and 15 the tissue P_{O_2} showed very little difference between normoxic and hypoxic animals.

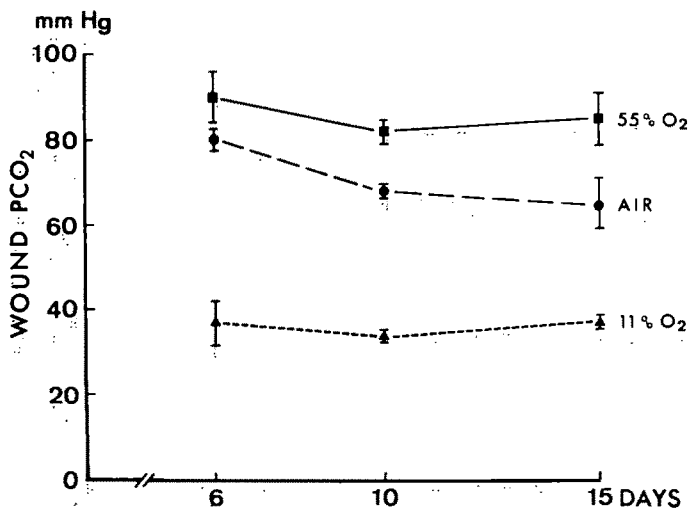


FIG. 2. Effect of changes in inspired oxygen tension on wound P_{CO_2} . For values of each observation day $P < 0.01$; analysis of variance.

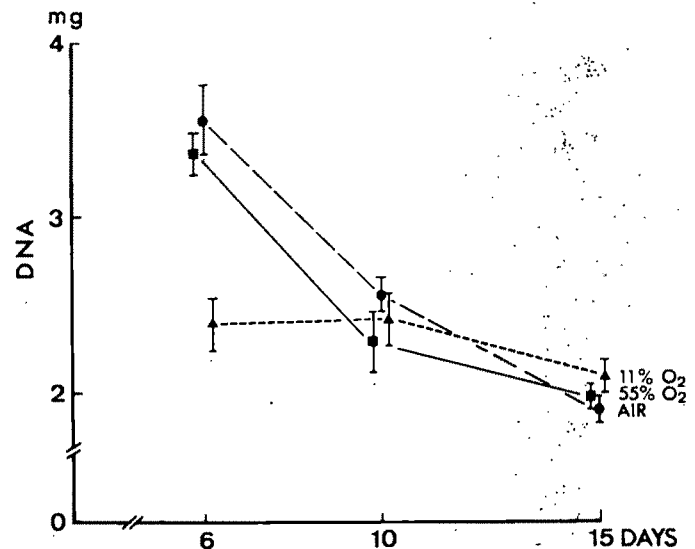


FIG. 3. Effect of changes in inspired oxygen tension on the amount of wound DNA.

The higher the inhaled oxygen concentration the higher the wound P_{CO_2} (Fig. 2). The mean tissue P_{CO_2} varied between 82 and 90 mm Hg in 55% O_2 , between 65 and 80 mm Hg in air and between 34 and 37 mm Hg in 11% O_2 .

Six days after implantation the amount of wound DNA in the hypoxic group was approximately 30% lower than the values in normoxic and hyperoxic animals (Fig. 3; $P < 0.001$; t -test). On the days 10 and 15 these differences were no longer observed.

The amounts of collagen hydroxyproline rose gradually in all groups as healing progressed (Fig. 4). The sharpest rise took place between days 6 and 10. On the 15th day the values in hypoxia remained significantly below the control level ($P < 0.05$).

In general, the amounts of adenosine phosphates increased gradually as healing progressed. The AMP concentration (Fig. 5) was not affected by changes in oxygen supply. On days 10 and 15 the highest wound ADP concentrations were observed in rats breathing 55% O_2 and the lowest concentrations in rats breathing 11% O_2 (Fig. 6). However, the only statistically significant difference in ADP levels was on the day 15, between normoxic and hypoxic wounds ($P < 0.01$). The results of ATP determinations (Fig. 7) were comparable with the changes of ADP. The highest wound ATP concentrations were observed in 55% O_2 on day 10 ($P < 0.001$ vs air group). In hypoxia the ATP levels remained clearly below the controls ($P < 0.01$ for 15-day wounds).

The highest capacity for glucose consumption by the repair tissue was observed on the 10th day in all groups (Table 1). At this phase animals kept in hypoxia showed significantly retarded capacity for utilization of glucose under the standard test conditions ($P < 0.05$). The ex vivo rates of lactate production (Table 1) were comparable with the rates of glucose consumption. In implants removed

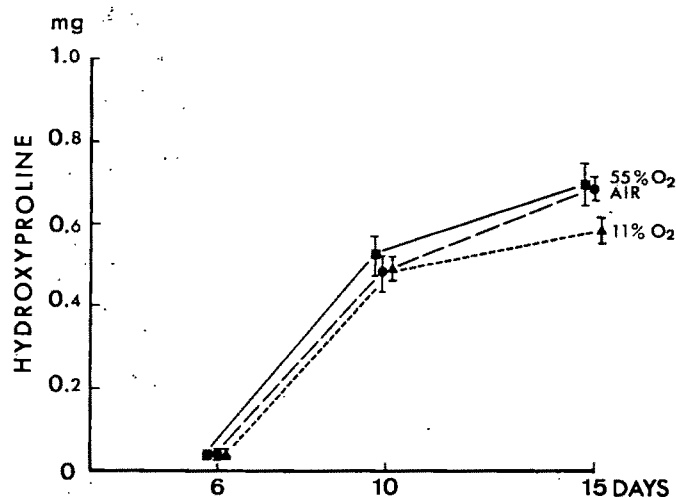


FIG. 4. Effect of changes in inspired oxygen tension on the amount of wound collagen hydroxyproline.

from hypoxic rats on day 10 the lactate production was 55% below the control level ($P < 0.001$). The capacity for oxygen consumption (Table 1) behaved similarly in control and hyperoxic groups, increasing sharply between days 6 and 10 and remaining unchanged thereafter. In tissues taken from hypoxic animals oxygen utilization increased more slowly ($P < 0.05$ for 10-day implants) and reached the control level first on the 15th day.

Discussion

Oxygen kinetics in healing wounds gained increasing attention after it was shown that repair processes respond to changes in oxygen supply.^{7,8,12} In several types of wounds increased oxygen tensions enhance healing and, conversely, reduction in available oxygen inhibits tissue repair.^{10,11,15,18,20} In experimental wounds containing a large dead space the accumulation of collagen is roughly

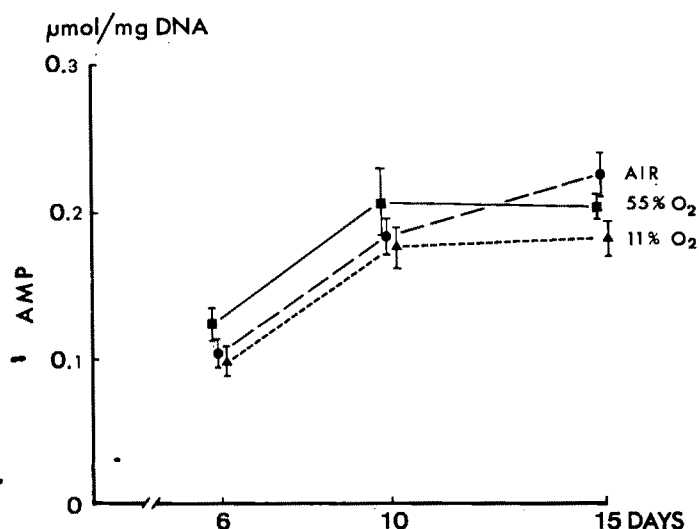


FIG. 5. Effect of changes in inspired oxygen tension on the concentration of wound AMP.

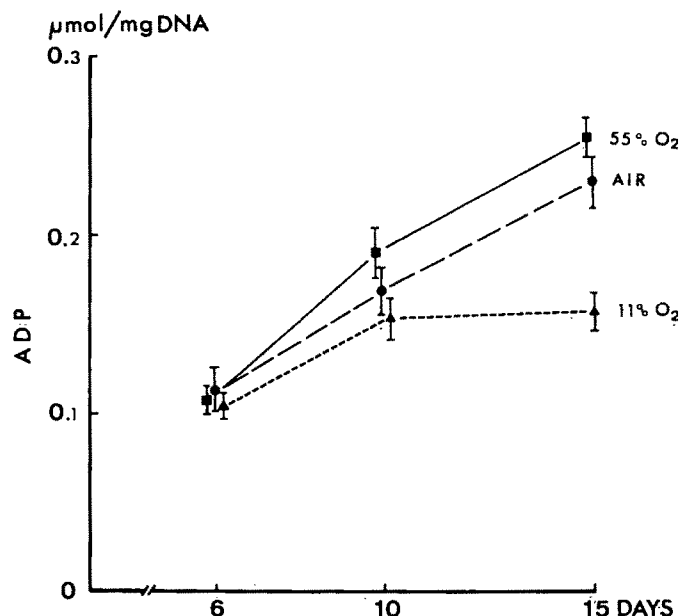


FIG. 6. Effect of changes in inspired oxygen tension on the concentration of wound ADP.

proportional to the arterial blood P_{O_2} at nontoxic ambient oxygen tensions.^{8,12}

Studies with cylindrical cellulose sponge implants indicated that the Pasteur effect pertains to healing wounds.²¹ Hyperoxia shifts the wound metabolism towards aerobic glycolysis and activates the citric acid cycle. The activity of succinate dehydrogenase, a linking enzyme between citric acid cycle and electron transfer chain, also increases with increasing oxygen supply.

The large size of cellulose sponge implants used in studies of wound healing creates a considerable dead space.^{8,12,22} The granulation tissue grows slowly from the

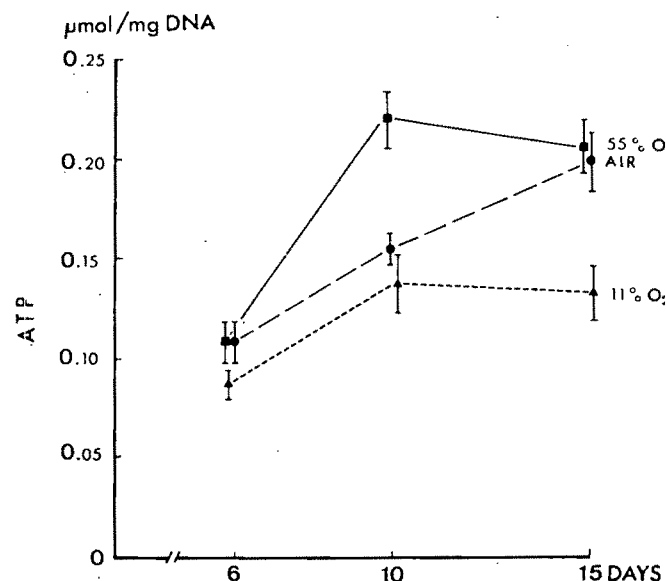


FIG. 7. Effect of changes in inspired oxygen tension on the concentration of wound ATP.

TABLE 1. *Glucose Utilization, Lactate Production and Oxygen Consumption in Tissues Taken From Wounds Healing in Various Oxygen Environments and Tested ex vivo in Air*

Group	Glucose consumption $\mu\text{mol/mg DNA/hr}$			Lactate production $\mu\text{mol/mg DNA/hr}$			Oxygen consumption $\mu\text{l/mg DNA/hr}$		
	6 dys	10 dys	15 dys	6 dys	10 dys	15 dys	6 dys	10 dys	15 dys
11% O ₂	0.41 ± 0.17	0.83 ± 0.16	0.73 ± 0.12	0.69 ± 0.11	2.00 ± 0.39	3.19 ± 0.30	56 ± 21	89 ± 22	159 ± 3
Air	0.63 ± 0.12	1.74 ± 0.18	0.80 ± 0.17	1.53 ± 0.11	4.28 ± 0.32	3.38 ± 0.17	86 ± 17	178 ± 17	174 ± 14
55% O ₂	0.62 ± 0.19	1.39 ± 0.21	0.76 ± 0.19	1.04 ± 0.12	4.62 ± 0.33	2.80 ± 0.09	66 ± 17	139 ± 10	183 ± 18

Each figure represents the mean $\pm$ S.E.M. of 8 wounds

periphery of the implant towards the central dead space and the sequences of healing overlap each other. Thus the outer layers usually contain mature collagen fibers whereas in more central parts the cellular inflammatory reaction is still progressing. In the present model the matrix was only 2.5 mm thick and the tissue ingrowth occurred mainly from two opposite directions. This ensured that there was more granulation tissue of the same phase in different parts of the implant.

It has been demonstrated that when arterial P_{O_2} is elevated the mean capillary P_{O_2} rises, more oxygen reaches wound tissue and the capillary-tissue oxygen gradient increases.^{14,17} The present findings of tissue oxygen tensions fully agree with this concept. In thin implants the average tissue P_{O_2} clearly exceeded that reported in dead space wounds.^{8,14,21} This is probably due to decreased diffusion distance for oxygen from the supplying capillary. The wound P_{O_2} in rats breathing 55% O₂ gradually decreased from the 6th day onwards (Fig. 1). This might result from increasing oxygen consumption, diminishing vascularization of the sponge or impaired oxygen diffusion through the developing collagenous stroma.

The increase in wound P_{CO_2} with increasing respiratory oxygen tension was a constant finding on each observation day (Fig. 2). The high tissue P_{CO_2} values in hyperoxia could be ascribed to enhanced production of carbon dioxide, oxygen-induced vasoconstriction, hypoventilation, decreased carbon dioxide-carrying capacity of hemoglobin or changes in vascular pattern. Reverse phenomena may account for the decreased wound P_{CO_2} in hypoxic rats.

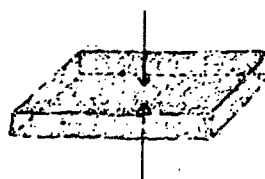
Early cellular invasion and proliferation resulted in rapid accumulation of DNA in implants of normoxic and hyperoxic rats (Fig. 3). Hypoxia appeared to inhibit cellular proliferation. Between days 6 and 10 the proliferative phase subsided and the amount of collagen increased sharply.

The amounts of collagen hydroxyproline showed very little variation between the different groups (Fig. 4). Only the 15-day values of hypoxic rats were clearly below the control level. This suggests that the local oxygen tension was generally sufficient for adequate collagen synthesis even in hypoxic animals in which the lowest mean P_{O_2} was

18 mm Hg. The findings agree with earlier measurements of wound oxygen tensions according to which collagen synthesis appears to diminish as oxygen tension drops below a critical level at about 15 mm Hg.¹⁷ In large dead space wounds the rate of collagen accumulation has been directly proportional to arterial blood P_{O_2} , probably because their oxygen tensions remain below 15 mm Hg under normal

WOUND MODEL

2.5 x 14 x 20 mm IMPLANT
(SMALL DEAD SPACE)



10 x 10 x 20 mm IMPLANT
(LARGE DEAD SPACE)

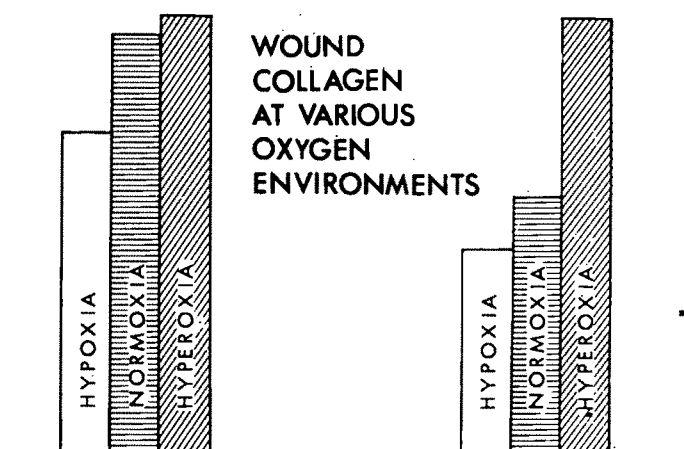
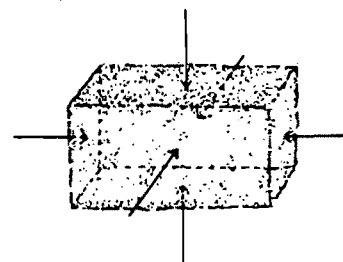


FIG. 8. Scheme summarizing the influence of implant size on collagen accumulation at various oxygen environments. Data of thick implants are from an earlier work.¹²

conditions and even in moderate hyperoxemia.⁸ Obviously, vascular network fills the thin sponge implant within a few days. This reduces tissue hypoxia and decreases the need for additional oxygen. In large dead space wounds the situation is different (Fig. 8); to achieve optimal healing the supply of oxygen must be markedly increased.

Cellular respiration is controlled by substrate level, oxygen supply, ADP concentration and by the capacity of respiratory chain.⁵ If oxygen is lacking the energy metabolism uses more substrates, the supply of which may become rate-limiting. Oxygen economizes substrate use and, if the supply of oxygen is sufficient, the control of respiratory rate is shifted to ADP or the respiratory chain. The present data suggest that the effect of oxygen on wound energy metabolism is not limited to saving of substrates since the amounts of ADP increased with increasing oxygen tension (Fig. 6). Succinate dehydrogenase of healing wounds is elevated in hyperoxia denoting an increased capacity of electron transfer chain.²¹

The concentrations of ATP in repair tissue also responded to changes of local oxygen tension (Fig. 7). Since hyperoxia abolished several limiting factors in energy production the high concentration of ATP in hyperoxic wounds is not due to reduced consumption of chemical energy but corresponds to a new level at which both energy production and use are elevated. Presumably the effects of hypoxia are the converse.

The experiments on the capacity for glucose and oxygen consumption and lactate production were carried out *in vitro* with air as the oxygen source. Thus the P_{O_2} of the medium was 150 mm Hg, and therefore, the wound tissues, accustomed to artificial atmospheres, were now being tested at an oxygen tension far higher than they had ever experienced before. Although the diameter of the tissue slices was less than 0.4 mm, these slices are large enough to necessitate large oxygen gradients even in tissue incubated in air. Therefore, there has to be some reservation about the quantitative changes measured by this method. It is possible that the various oxygen environments had produced sufficient changes in the tissue to influence the results in a manner that cannot be predicted.

In general the capacity for glucose utilization, lactate production and oxygen consumption was decreased in tissues taken from hypoxic animals (Table 1). Since all the incubations were carried out at the same atmosphere it is suggested that in hypoxic wounds the low P_{O_2} is not necessarily the only limiting factor in wound energy production. Low ADP concentrations and depressed succinic dehydrogenase levels in hypoxic wounds²¹ further support this concept.

It is concluded that reduction of tissue oxygen supply by systemic hypoxia has a detrimental effect on wound energy metabolism. Measurements of wound oxygen tensions agree with earlier findings according to which retarded

healing occurs as the P_{O_2} declines below a critical level of 15 to 20 mm Hg. Increase of P_{O_2} over this critical level did not accelerate healing.

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Choice of Abdominal Operative Incision in the Obese Patient: A Study Using Blood Gas Measurements

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Although many factors may influence the choice of the operative incision, physiologic safety in terms of the degree of postoperative hypoxemia should be considered. No data currently exist to delineate in markedly obese patients the effect of the operative incision on the extent or duration of this hypoxemia. Fifty-four consecutive patients of both sexes, scheduled for elective jejunoileal bypass for morbid exogenous obesity, were studied. In 23 patients the operation was performed through a transverse incision and in 25 patients through a vertical incision. In 6 other patients, cholecystectomy was also performed in addition to the jejunoileal bypass. Postoperatively there was a significant fall in Pao_2 both in the transverse and vertical incision groups and this continued through day 4. On day 5 statistically significant hypoxemia was present only in the vertical incision group. In addition, the decrease in Pao_2 was significantly greater on days 4 and 5 in the vertical group than in the transverse group. On days 2 and 3 again the mean decrease in Pao_2 was greater in the vertical group but this was not statistically significant. The effect of added cholecystectomy on Pao_2 was studied in 6 women with midline incisions. The results were compared with 6 subjects who had small bowel bypass without cholecystectomy and who were matched for incision, age, weight, girth/height ratio, weight/height ratio, smoking habit, and percentage of predicted ERV. In both groups there was a significant fall of Pao_2 from day 1 through day 4, but there was no significant difference between the two groups. Although the numbers studied were small, these limited results would suggest that the type of incision rather than the intraoperative procedure is the important factor in determining postoperative Pao_2 changes. These studies also suggest that in patients with an increased potential for postoperative hypoxemia (i.e. markedly obese), the transverse abdominal approach should always be seriously considered.

A PROPERLY PLANNED incision is fundamental to the performance of any operative procedure. A good abdominal incision is one which can be made relatively rapidly, affords accessibility, extensibility, and provides the greatest strength to the abdominal wall (i.e. least subject to wound dehiscence or later herniation). Assessment of the abdominal incision with regards to patient safety as well as convenience is also important. Finally, a good cosmetic result consistent with the above considerations should be a goal.

The type of incision should suit the particular case. For abdominal trauma the vertical midline incision is the most satisfactory; it can be rapidly made, is easily extended from xiphoid to pubis, and if necessary, can be combined with a thoracic extension for abdominothoracic exposure. Additional lateral exposure may readily be obtained by a transverse extension to any level.

In elective surgery, especially in obese patients, one might seriously consider the transverse abdominal approach. Abdominal closure is both easier and more secure with this approach, because wound approximation tends to occur when the patient coughs and/or strains. Many factors should influence the choice of incision not the least of which are the build of the patient and the probable accuracy of the preoperative diagnosis. No data are currently available in markedly obese subjects to ascertain the physiologic safety of the operative incision. The purpose of this paper is to examine the relationship of the abdominal incision to the postoperative fall in arterial oxygen tension in markedly obese patients.

Materials and Methods

Fifty-four consecutive patients of both sexes, scheduled for elective jejunoileal small bowel bypass for morbid exogenous obesity, were included in this study. Routine preoperative tests relevant to this study included electrocardiogram, chest roentgenogram, blood pressure, pulse, and selected pulmonary function tests. No patient had clinical evidence of cardiopulmonary disease preoperatively. In 23 patients the operation was performed through a supraumbilical transverse incision and in 25 patients through a vertical paramedian or midline incision. The details of the bypass are depicted diagrammatically in Figure 1. In 6 other patients, cholecystectomy was also

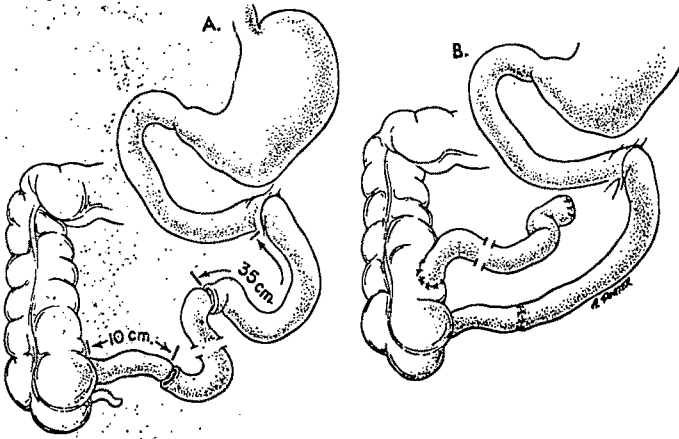


FIG. 1. Jejunioileal bypass as performed by the authors.

performed in addition to the jejunioileal bypass; the approach in each of these patients was via a vertical midline incision.

Arterial blood gases were sampled a few days before operation with the unsedated patient breathing room air in the sitting position for 15 minutes. All postoperative arterial blood gas samples were obtained (after breathing room air for 15 minutes) with the patient in the semi-recumbent position in bed. Blood samples were obtained anaerobically from the radial artery by direct puncture after infiltration of the skin with 0.5% lidocaine or from an indwelling intra-arterial cannula. Arterial blood was collected into iced plastic syringes containing heparin and analyzed within 5 to 10 minutes by the same technician in our research laboratory. An Instrumentation Laboratory Model 213 blood gas analyzer was used to analyze P_{aO_2} , P_{aCO_2} , and pH, and the raw data corrected, when appropriate for patient-electrode temperature difference.⁷

Preoperatively, expiratory reserve volume (ERV), corrected to body temperature and pressure fully saturated (BTPS), was measured in the seated position using a spirometer. Girth was measured in the standing position at the level of the umbilicus at normal end (resting) exhalation.

Preoperative premedication consisted of Innovar 2 cc and diphenhydramine hydrochloride 50 mg given I M 60 to 90 minutes before induction of anesthesia. Pretreatment was with gallamine (20 mg) given 3 to 5 minutes before induction of anesthesia. Induction was with sodium thiopental (250 to 600 mg) followed by succinylcholine (100 to 120 mg) to facilitate endotracheal intubation with a cuffed tube. Anesthesia was maintained with 60% nitrous oxide, 40% oxygen, and 0.5 to 1.0% halothane, supplemented with pancuronium as need for muscle relaxation. Respiration was controlled with a tidal volume of 8 to 10 ml per kg estimated lean body weight at a rate of 10 to 12 per minute. The effect of the muscle relaxant was antagonized with neostigmine (0.06 mg/kg) at the

end of the operation, while the muscarinic effects of the latter were blocked with atropine (0.02 mg/kg).

Adequate reversal of muscle relaxant effects was determined by noting sustained tetanus for 5 seconds at 50 Hertz using a peripheral nerve stimulator, by ability to lift the head from the pillow, by measuring negative inspiratory force, and ability to open the eyes and obey commands. The overall mean duration of anesthesia was 226.5 minutes. After emergence from anesthesia, each patient was observed in the postoperative anesthesia recovery (PAR) area for 2 to 4 hours before being transferred to the surgical intensive care unit.

With vital signs stable and the patient able to respond to commands, arterial blood gas measurements during breathing room air were obtained in the recovery area 2 to 4 hours after the operation. Narcotic medication was not given until these studies had been completed. Neither severe shivering nor marked deviation from normal body temperature was present during these measurements. All subsequent postoperative measurements were made at least 4 hours after any narcotic medication or respiratory therapy treatments. Blood gas values were obtained each morning, usually between 8 and 10 A.M.

Collected data was analyzed with an analysis of variance to ascertain variance within and among different groups. Subsequently, a paired *t*-test was employed to test the difference in means between groups. Comparison of the latter with the former analysis served to check any variation within groups. Chi-square analysis was performed to check sex ratio differences between groups.

Results

Forty-eight patients were divided into two groups on the basis of the type of operative incision: Group I had a supraumbilical transverse incision ($n=23$) and Group II had a midline vertical incision ($n=25$). Only a jejunioileal bypass, appendectomy, and routine liver biopsy were performed on these two groups of patients. There was no significant difference between Groups I and II with respect to age, sex distribution, weight, girth, height, girth/height ratio, weight/height ratio, smoking history, duration of anesthesia, and percentage of predicted expiratory reserve volume (ERV). These data are presented in Table 1.

Six other female patients with vertical incision, in addition to jejunioileal bypass, appendectomy, and liver biopsy, also underwent simultaneous cholecystectomy for cholelithiasis. Table 2 presents these 6 women (Group II-B) matched according to age and girth/height ratio with 6 women (Group II-A) from Group II. There was no significant difference between Groups II-A and II-B with respect to age, weight, girth/height ratio, weight/height ratio, smoking history, duration of anesthesia, and percentage of predicted ERV (Table 2).

TABLE 1. Physical Characteristics of 48 Patients With Jejunoileal Bypass Only:
Group I (Transverse Incision) and Group II (Mid-line Incision)

Group	No. of Pts.	Sex F/M	Age* (yrs)	Weight* (kg)	Girth* (cm)	Height* (cm)	G/Ht* ratio	Wt (kg)* Ht (cm) ratio	ERV* (% pre- dicted value)	Smoking** Habit (pack- years)	Duration of Anesthesia (min)
I. Supra- umbilical Transverse Incision	23	18/5	33.8 ± 8.2	144.2 ± 23.4	147.1 ± 14.4	168.2 ± 7.4	0.876 ± .095	0.859 ± .139	50.2 ± 23.6	7.7 ± 12.0	212 ± 27.1
II. Vertical Incision	25	22/3	34.0 ± 7.1	150.7 ± 36.4	149.0 ± 19.8	168.9 ± 8.2	0.882 ± .111	0.890 ± .187	62.0 ± 18.4	7.6 ± 13.9	241 ± 34.7
Significance of Difference Between I and II		NS	> 0.9	> 0.4	> 0.5	> 0.5	> 0.5	> 0.5	> 0.1	> 0.9	> 0.5

*Values represent mean ± standard deviation.

**Pack-Years = number of packs of cigarettes per day times the number of years smoking that amount.

The postoperative changes in arterial oxygen tension (P_{aO_2}) within Groups I and II are presented in Table 3 and Fig. 2. When mean postoperative P_{aO_2} measurements were compared with control (preop) P_{aO_2} values, there was a significant fall in both Groups I and II beginning in the postoperative recovery room (PAR) and continuing through day 4 in Group I (transverse incision) and day 5 in Group II (vertical incision). When the mean decrease in P_{aO_2} was compared (postop-preop) between Groups I and II (Table 4), there was a difference between Group I (transverse incision) and Group II (midline incision) on postoperative days 4 and 5. Patients with vertical incision (Group II) manifested a greater fall in P_{aO_2} on days 4 and 5 when compared with Group I patients. In addition, this reduced P_{aO_2} had not returned to preoperative control levels by day 5 (Fig. 2). Using an analysis of variance, there was an identifiable variance within each group, but this internal variability could not explain the observed difference seen between Groups I and II on postoperative days 4 and 5.

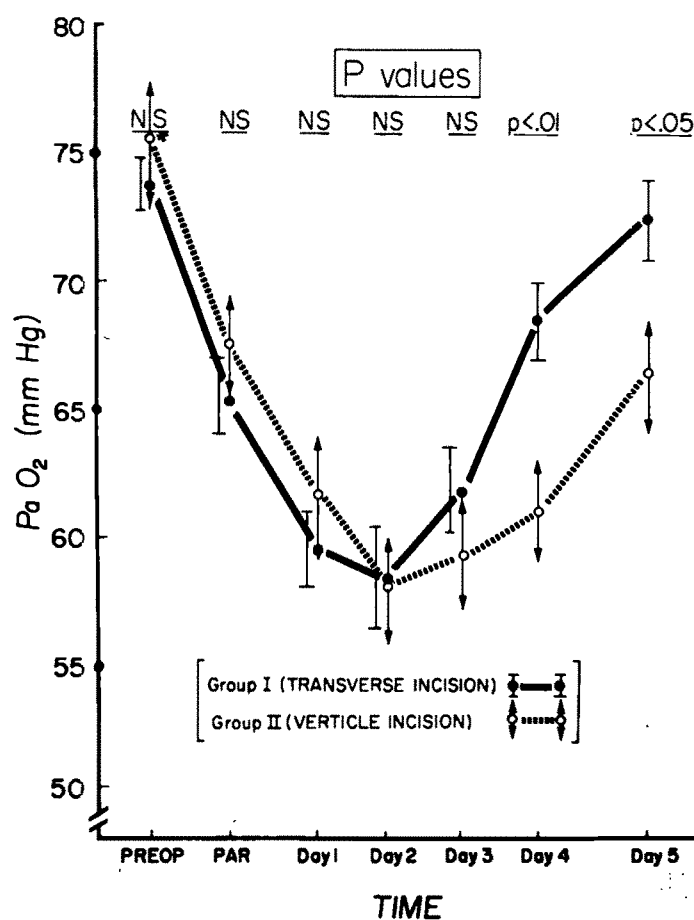


FIG. 2. Graphic presentation of the fall in P_{aO_2} (mm Hg) with time postoperatively. Each point represents the mean of the values for 23 patients in Group I (solid line) or 25 patients in Group II (interrupted line) with appropriate ± standard error of the mean (SE).

TABLE 2. *Physical Characteristics of Six Female Patients with Mid-line Incision Plus Cholecystectomy (Group II-B) Compared With Six Female Matched Patients with Mid-line Incision Without Cholecystectomy (Group II-A)*

Group	No. of Pts.	Age (yrs)	Weight* (kg)	Girth/* Height Ratio	Weight* Height Ratio	ERV* (% predicted value)	Smoking** Habit (Pack/Yrs)	Duration of Anesthesia (min.)
II-A Vertical incision without cholecystectomy	6	40.0 ±10.1	142.2 ± 21.6	0.879 ±0.115	0.852 ±0.137	51.2 ±22.0	18.8 ±24.0	237 ± 38.3
II-B Vertical incision with cholecystectomy	6	40.5 ±11.3	134.3 ± 24.7	0.912 ±0.116	0.833 ±0.173	49.9 ±20.9	4.2 ± 6.6	270 ± 31.4

*Values represent mean ± standard deviation

**Pack-years = number of cigarettes per day times the number of years smoking that amount.

The possible effect of an added cholecystectomy (upper abdominal surgery) on the change in P_{aO_2} was studied by comparing two groups with the same vertical incision, matched as presented in Table 2. The postoperative changes in P_{aO_2} within each group are presented in Table 5. Comparing mean postoperative P_{aO_2} measurements with control preoperative values, there was a significant decrease in P_{aO_2} in both Groups (II-A and II-B) beginning in the PAR and continuing through day 5. When the mean reduction in P_{aO_2} (postop-preop) was compared between Groups II-A and II-B (Table 6), there was no significant difference between these two subgroups. This inability to demonstrate an added effect of upper abdominal surgery (cholecystectomy) on P_{aO_2} could possibly be due to the small sample size.

Although arterial P_{CO_2} was measured with each P_{aO_2} determination, there was no significant difference in the postoperative values from control preoperative values. Furthermore, on statistical analysis we did not demonstrate significant differences between this variable either within or between groups.

Clinical findings of cough, increasing sputum production

or change in character of the sputum, bronchospasm, or change in chest roentgenogram (preop to postoperative studies) were not present in any of the 54 patients. However, 91% of the patients developed an elevation of rectal temperature of 0.5 to 1.5 degrees centigrade over the first 2 to 6 days postoperatively which resolved with increasing ambulation.

Discussion

The choice of the type of abdominal operative incision in the obese patient can be examined under two headings: technical and pulmonary considerations. Since the obese individual is at a higher risk with respect to postoperative pulmonary complications,^{5,29} an assessment of the pulmonary gas exchange with different incisions would seem to be useful.

A. Technical Considerations

The factors which should be considered for a good abdominal incision are: 1) *Rapidity* (i.e., should be easy to perform and close). Vertical incisions are quicker to make and quicker to close than transverse incisions. 2) *Accessi-*

TABLE 3. *Arterial Oxygen Tension Measurements (Room Air) at Various Times in Groups I and II*

Time	P_{aO_2} * (mm Hg)	Group I (n = 23)		P_{aO_2} * (mm Hg)	Group II (n = 25)	
		Mean difference from control in mm Hg (postop-preop)	Significance of difference (P value)		Mean difference from control in mm Hg (postop-preop)	Significance of difference (P value)
Preop control (sitting)	73.9 ± 5.1	—	—	75.6 ± 9.5	—	—
Postop PAR**	65.1 ± 7.7	- 8.8	< .001	67.6 ± 9.0	- 8.0	< .001
Day 1	59.4 ± 8.5	-14.5	< .001	61.8 ± 9.7	-13.8	< .001
Day 2	58.4 ± 9.0	-15.5	< .001	58.5 ± 10.6	-17.1	< .001
Day 3	61.8 ± 8.8	-12.1	< .001	59.2 ± 11.1	-16.4	< .001
Day 4	68.5 ± 7.5	- 5.4	< .001	61.0 ± 10.7	-14.6	< .001
Day 5	72.3 ± 6.9	- 1.6	NS†	66.5 ± 11.6	- 9.1	< .001

*Values represent mean ± standard deviation.

**Postanesthetic recovery (2-4 hours postop).

†Not statistically significant.

TABLE 4. Comparison of Mean Reduction in P_{aO_2} (Postop-Preop) in Group I versus Group II

Time Postop	PAR* (2-4 hrs)	Day 1*	Day 2*	Day 3*	Day 4*	Day 5*
Group I	-8.8	-14.5	-15.5	-12.1	-5.4	-1.6
Group II	-8.0	-13.8	-17.1	-16.4	-14.6	-9.1
Significance (P value)	NS†	NS†	NS†	NS†	P<0.01	P<0.05

*All values are mean differences from control in mm. Hg.

†Not significant.

bility (exposure). Transverse incisions provide equal exposure to vertical incisions for most intra-abdominal structures. 3) *Extensibility*. This is excellent with vertical incisions, but is less adequate with the transverse approach, unless the latter is combined with a vertical extension. 4) *Strength* (i.e., cause no weakness to the abdominal wall; therefore, should not be followed by wound dehiscence or late herniation). For maximum strength, surgical incisions should be made parallel rather than perpendicular to normal lines of stress. By a rather crude method, Sloan²³ found that in patients under light anesthesia the strain upon a vertical incision is about thirty times as great as that on a transverse incision. Vertical incisions tend to be separated by abdominal muscle contraction, while transverse ones tend to be closed down to a slit. Wound disruption is a rare, but serious complication of laparotomy. Its incidence is about 1%,¹⁰ with an average mortality of about 15%.¹⁹ Singleton found the wound disruption rate following vertical incisions was twenty times more frequent than that following transverse incisions.²² Keill and co-workers also found that dehiscence was more likely to occur through transverse than through vertical incisions.¹⁷ Upper midline incisions disrupt more frequently than lower midline incisions.²⁷ Basically, the two reasons for abdominal wound disruption are:^{11,21} (a) the intra-abdominal pressure is excessive due to such causes as coughing, vomiting, distension, hiccupping, straining of the closure at the end of operation or straining during micturition or defecation, and

(b) the wound is intrinsically weak. This may be due to general causes (such as hypoproteinemia, anemia, vitamin C deficiency, administration of steroids, gross edema, uremia, and/or irradiation) or to local causes (such as sepsis, hematoma, or ischemia). 5) *Minimal postoperative pain*. It is the impression of many surgeons that vertical incisions are more painful in the immediate postoperative period and consequently interfere with coughing. In Halasz's study,¹⁶ patients with transverse incisions required significantly less analgesics in the postoperative period than patients with vertical incisions. The amount of analgesic given is very important since inadequate analgesia will result in inadequate coughing and deep breathing while excessive analgesia may sedate the patient to the point of hypoventilation and abolish the sighing mechanism.¹² 6) *Good cosmetic result*. It is the current opinion that incisions parallel with the wrinkle lines (i.e. a transverse abdominal incision) give the best cosmetic result.¹⁸

B. Pulmonary Considerations

Pulmonary complications continue to be one of the most significant problems following laparotomies. Both Churchill and McNeill⁸ and Beecher³ demonstrated a significant decrease of the vital capacity (VC) after abdominal operations. Beecher showed that the decrease is more marked after upper rather than after lower abdominal operations. This reduction in VC connotes

TABLE 5. Arterial Oxygen Tension Measurements (Room Air) at Various Times in Group II-A and Group II-B

Time	P_{aO_2} * (mm Hg)	Group II-A (n = 6)	Significance of difference (P value)	P_{aO_2} * (mm Hg)	Group II-B (n = 6)	Significance of difference (P value)
		Mean difference from control in mm Hg (postop- preop)			Mean difference from control in mm Hg (postop- preop)	
Preop						
Control (sitting)	72.0 ± 8.9	—		74.0 ± 5.0	—	
Postop						
PAR**	62.3 ± 9.4	-9.7	< .01	67.8 ± 5.5	-6.2	< .001
Day 1	56.2 ± 8.4	-15.8	< .001	55.7 ± 6.3	-18.3	< .001
Day 2	53.8 ± 5.3	-18.2	< .01	54.3 ± 6.9	-19.7	< .001
Day 3	54.5 ± 7.0	-17.5	< .01	60.6 ± 5.3	-13.4	< .001
Day 4	58.5 ± 7.0	-13.5	< .01	64.7 ± 9.5	-9.3	< .02
Day 5	64.2 ± 7.0	-7.8	< .02	65.3 ± 6.1	-8.7	< .02

*Values represent mean ± standard deviation.

**Postanesthetic recovery (2-4 hours postop).

TABLE 6. Comparison of Mean Reduction in P_{aO_2} (Postop-Preop) in Group II-A versus Group II-B

Time	PAR*	Dy 1*	Dy 2*	Dy 3*	Dy 4*	Dy 5*
Postop	(2-4 hrs)					
Group II-A	-9.7	-15.8	-18.2	-17.5	-13.5	-7.8
Group II-B	-6.2	-18.3	-19.7	-13.4	-9.3	-8.7
Significance (p value)	NS†	NS†	NS†	NS†	NS†	NS†

*All values are mean differences from control in mm Hg.

†Not significant.

both a decrease in pulmonary reserve and, if less than 10 ml/kg, an ineffective cough.⁴

Transverse incisions have significantly fewer pulmonary complications than vertical ones.² In Rees and Collier's series²⁰ pulmonary complications occurred almost four times more frequently in the vertical than in the transverse group. Halasz¹⁶ in his prospective, randomized series of 100 patients with vertical and transverse laparotomies found that 20% of the patients with vertical incisions developed significant pulmonary complications (pneumonia or atelectasis demonstrated by radiography), as compared with only two per cent in the transverse group. Minor episodes of fever which responded to coughing or nasotracheal suction were not included. Using the above definition, there were no significant pulmonary complications in any of our patients. However, there was a more significant and more prolonged hypoxemia in the vertical as opposed to the transverse group. The basis for the hypoxemia is probably a reduction in lung volume, not demonstrable by chest radiography. This reduced lung volume is probably the result of incisional pain.^{13,14} In the early postoperative period, due to the patient's subconscious effort to minimize pain, the abdomen is splinted and as a result the diaphragmatic excursions are impaired, which results in a decrease in vital capacity.³ This response to abdominal pain favors the development of hypoxia and "patch miliary atelectasis." The reduction of postoperative pain and splinting, along with better pulmonary and cough efficiency with the transverse incision may serve to decrease the incidence of pulmonary complications.

In previous studies we have demonstrated that preoperatively there was a significant reduction in arterial oxygen tension in obese patients when compared with control patients matched for age and that during the postoperative days 1 through 4, there was a further fall in P_{aO_2} which often reached dangerous levels. The minimum postoperative P_{aO_2} could be best predicted by the girth/height or weight/height ratios.²⁸

In 1967 Dollfuss et al.⁹ suggested that during expiration from total lung capacity to residual volume, a point was reached where a significant amount of small airways in the dependent regions of the lung were closed with consequent alveolar gas trapping; this volume was termed the closing volume (CV). Postoperatively, with spasm of the expira-

tory muscles, the functional residual capacity (FRC) will be reduced at the expense of ERV. Resting ventilation will take place at a lower lung volume and airway closure will occur earlier during expiration (i.e., within the tidal volume range).^{1,24}

The nature of the intrapulmonary disorder responsible for the hypoxemia is not clear. Diamant and Palmer⁸ suggest that a frank shunt through non-ventilated or atelectatic lung tissue is the most important factor, whereas others^{15,26} believe that a ventilation/perfusion disturbance (which arises from excessive perfusion or underventilation of pulmonary alveoli) is the most important factor. In fact it is likely that the postoperative functional pulmonary lesions involve a spectrum of changes. In mild cases, unevenness of ventilation is the main disturbance, while progression to alveolar collapse with further reduction in lung volume, and a frank shunt is the worst extreme.²⁵

In conclusion, our results show a more significant and prolonged reduction in arterial oxygen tension in the vertical as opposed to the transverse incision group. These results were obtained in an obese but otherwise healthy group of elective surgical patients. One might expect even more severe postoperative hypoxemia in an older, markedly obese patient with a history of cigarette smoking. Consequently, surgical convenience should be carefully weighed against physiologic safety when planning the surgical incision for these high risk patients.

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Influence of Vitamin A on Wound Healing in Rats with Femoral Fracture

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Groups of healthy wounded rats with and without comminuted femoral fractures, and maintained on nutritionally complete commercial rat chow with and without supplemental vitamin A, were studied. The test wounds were standard dorsal skin incisions and s.c. polyvinyl alcohol sponge implants. In some experiments the rats were pair-fed; the rats with femoral fracture not receiving supplemental vitamin A were the lead group for determining food allowances. In other experiments, the rats were allowed food *ad libitum*. We found that wound healing of rats with femoral fracture was increased when supplemental vitamin A was given, but the supplemental vitamin A did not completely obviate the adverse effects of fracture. The ratio of the breaking strengths of the skin incisions after formalin fixation to the breaking strengths of the incisions in the fresh state was higher in the un-supplemented rats, supporting the results of our earlier experiments that vitamin A increases the rate of collagen cross-linking.

The injured patient must heal his wounds for successful recovery, but it is the patient with extensive injury who may have the greatest difficulty in doing so. The experimental evidence is clear that wound healing is impaired in animals with severe injury.^{11,12} It is well documented that disturbances in the metabolism of protein, certain hormones and certain water-soluble vitamins, especially ascorbic acid, may occur after serious injury and thereby influence wound healing.^{7,10-12,16,18} Relatively little information regarding the metabolism of the fat-soluble vitamins after injury, and thereby their effects on healing in injured animals or patients, is available. Earlier studies in our laboratory, undertaken in rats mildly depleted on vitamin A and subjected to a skin

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incision and subcutaneous implants of polyvinyl alcohol sponges, suggested an increased requirement for vitamin A by such rats, since administration of vitamin A had a salutary effect on their survival, weight gain and the healing of their incisions and the formation of the sponge granuloma reparative tissue.¹⁴ We undertook the present study to determine whether this ameliorating effect of supplemental vitamin A on wound healing would be demonstrable in rats with an additional severe injury, namely, femoral fracture. An incidental aspect of the study was the determination of the effects of supplemental vitamin A on the liver and serum concentrations of vitamin A in injured rats.

Methods

The animals were male Sprague-Dawley rats* of approximately 325 gm body weight. The rats were kept individually in two-mesh steel cages at a room temperature of 22-25 C, and fed Rockland Mouse/Rat Complete Ration (meal)† and tap water.

Two experiments were performed on four groups of 12 rats. On four successive days, operations were performed with aseptic precautions by the same surgical team on groups of rats anesthetized with sodium pentobarbital (i.p.) supplemented with light ether anesthesia. Each rat received a 7 cm right paravertebral incision through the skin and panniculus carnosus. The wound was then undermined at three points to approximately 5 cm lateral to the skin edge by inserting Metzenbaum

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scissors at the upper, middle and lower poles, spreading the blades and tearing pockets between the superficial and deep muscles. A soft, water-moistened, sterile, porous polyvinyl alcohol sponge† (preweighed 22.0-22.9 mg) was then inserted into each pocket. Rats not selected for treatment with vitamin A received sponges containing 0.2 ml ethyl alcohol, while rats selected for oral and topical treatments with vitamin A received sponges containing 1 mg vitamin A,§ in 0.2 ml ethyl alcohol. The wound was then closed with 6 interrupted, evenly spaced, No. 36 stainless steel sutures. While still under anesthesia, 24 of the rats, Groups A and B, were subjected to a comminuted fracture of the right femur. This was done by making a small incision over the lateral aspect of the right thigh, separating the thigh muscles by blunt dissection and then closing a crushing clamp around the femur. The incision was closed with one stainless steel suture. All rats received a skin wound and 3 sponge implants. Half the animals received an additional injury, uni-lateral fracture of the right femur, and hereafter are designated as fracture groups of rats. Sutures were removed on the seventh postoperative day.

The rats of Groups B and C were pair-fed postoperatively according to the food intakes of Group A rats and Group D rats were pair-fed the food intakes of Group C rats for the corresponding postoperative day. Food intakes were measured daily and body weights determined every other day. The rats of Groups A and C were given orally each day 1 drop of peanut oil and their dorsal skin wounds anointed with 0.2 ml peanut oil for 7 days. Rats of Groups B and D were given orally each day 1 mg of vitamin A in 1 drop of peanut oil and 2 mg vitamin A in 0.2 ml peanut oil applied to their dorsal skin wounds starting promptly after operation and continued for 7 days. All animals were sacrificed by ether anesthesia on the 14th postoperative day.

†Unipoint Laboratories, High Point, North Carolina 27260.

§Crystalline vitamin A acetate, Eastman Kodak Co., Rochester, New York 14650.

In both experiments, the dorsal skin pelt was excised, restored as nearly as possible to its *in situ* dimensions on a multi-bladed cutter and then sectioned into seven 0.6 by 6.0 cm strips of skin. Cephalad strips 1, 2, and 4 were tested on a tensionometer for breaking strength in the fresh state and caudal strips 5, 6, and 7 were tested after 72 hours fixation in 10% buffered formalin. Strip 3 and the left sponge after excision were saved for histology. One of the sponges on the right side of the animals was analyzed for total hydroxyproline content by the method of Woessner¹⁹ and the remaining right sponge stored at 20 C. On the 11 day study of experiment 2, sections of the skin incisions and sponge granulomas were stained with hematoxylin-eosin as well as Mowry's colloidal iron stain for histologic study (including collagen and acid mucopolysaccharides) in a semi-quantitative manner.¹⁵ The slides were labeled by a code not known to the pathologist at the time of his examination.

The second experiment was a replicate of the first but all the rats were subjected to the additional injury of uni-lateral fracture of the right femur, were fed *ad libitum* postoperatively and sacrificed a few days earlier. Previous to sacrifice, blood was withdrawn from the heart while the rats were under ether anesthesia and sera were prepared. The livers were excised, weighed and wrapped in aluminum foil, and stored frozen at -20 C as were the sera, until analyzed for vitamin A by a modified Carr-Price method.¹

Results

Experiment 1

All the rats withstood the wounding and additional femoral fracture procedure except for one rat with fracture found dead 5 days after injury. The mean body weights of the pair-fed rat groups at operation and when sacrificed two weeks later are summarized in Table 2 along with the food intake data. The first two days after operation both fracture groups (A and B) lost about 6% of their body weight. This loss was substantially the same as

TABLE 1. Recapitulation

Experiment 1: Pair-fed				
Group*	Injury	Oral	Topical	Postop. Day Sacrificed
A	Incision/Fracture	Peanut oil	Peanut oil	14
B	Incision/Fracture	Vitamin A†	Vitamin A§	14
C	Incision	Peanut oil	Peanut oil	14
D	Incision	Vitamin A†	Vitamin A§	14
Experiment 2: Ad libitum-fed				
A ₂	Incision/Fracture	Peanut oil	Peanut oil	11
B ₂	Incision/Fracture	Vitamin A†	Vitamin A§	11
C ₂	Incision/Fracture	Peanut oil	Peanut oil	10
D ₂	Incision/Fracture	Vitamin A†	Vitamin A§	10

*12 rats per group.

†1 mg vitamin A acetate.

§2 mg vitamin A acetate.

TABLE 2. Body Weights and Food Intakes of Injured Rats, Some Given Oral and Topical Vitamin A

Experiment 1: Pair-Fed						
Group	Day	Wt. gm.*	Days	Postop. Intake†		Cals.
				Food	Prot.	
A. Peanut Oil Incision/Fracture	Operated	365 ± 3	2	5.9	1.5	20
	Sacrificed	386 ± 4	14	7.3***	1.8	25
B. Vitamin A Incision/Fracture	Operated	369 ± 3	2	5.5	1.4	19
	Sacrificed	397 ± 3§	14	6.9**	1.7	24
C. Peanut Oil Incision	Operated	371 ± 3	2	5.5	1.4	19
	Sacrificed	390 ± 3	14	7.2	1.8	25
D. Vitamin A Incision	Operated	369 ± 3	2	5.4	1.4	19
	Sacrificed	408 ± 3§	14	7.0‡	1.7	24

*Mean ± S. E. †Average food intake (gm/100 gm body wt) for first two days and entire postoperative period. Protein (gm/100gm body wt) equals 7 N determined by micro-Kjeldahl × 6.25. Calories/100 gm body wt estimated from manufacturer's ration composition. §Gained more weight than peanut oil group (P<0.01). **Lower food intake than peanut oil group (P = 0.05). ‡Lower food intake than peanut oil group (P<0.001). ***Pair-fed fracture rats given peanut oil ate more food than wounded rats given vitamin A (P<0.02).

found for wounded rats without fracture given peanut oil, whereas similar rats given vitamin A lost slightly less weight. Two weeks after operation fracture rats given peanut oil had gained 21 gm and those given vitamin A 28 gm. This 33% difference in weight gained by the vitamin A supplemented rats was significant (P<0.01). Wounded rats given peanut oil gained 19 gm for the same period, while those given vitamin A gained 39 gm. This two-fold difference in weight gain was likewise significant (p<0.01).

The first two days after operation all the injured rats ate 20-23% less food than during the remainder of the postoperative period. Thereafter, the food intake rose, reaching preoperative levels by the end of first week. Pair-feeding resulted in slightly lower food intakes (3-5%) for rats supplemented with vitamin A (Table 2).

Skin incisions of rats with fracture two weeks after

injury were found significantly stronger (19%, P<0.02) for rats given vitamin A than for rats given peanut oil when tested in the fresh state (Table 3). Among rats given vitamin A the skin wounds of rats without fracture were significantly stronger (25%) than wounds of fracture rats (P<0.001) and stronger (50%) than wounds of fracture rats given only peanut oil. The ratio of the formalin-fixed to fresh breaking strength of skin wounds was significantly lower for the vitamin A groups (P<0.02) suggesting an *in vivo* increase in cross-linking of the reparative collagen in the vitamin A supplemented rats.¹³

No difference in hydroxyproline content was found for the sponge granulomas of rats with or without fracture whether given peanut oil or vitamin A. However, among vitamin A treated rats, rats with fracture had significantly higher hydroxyproline contents (10%) in sponge-induced granulomas than wounded rats (P=0.02).

TABLE 3. Wound Strength and Sponge Granuloma Hydroxyproline of Injured Rats Given Oral and Topical Vitamin A: (Mean ± S.E.)

Experiment 1: Pair-Fed					
Group		Fresh	Breaking Strength, Gm. Formalin	Formalin Fresh	OHP (µg/100 mg sponge)
A. Peanut Oil Incision/Fracture	14 Days Postop	577 ± 38	2073 ± 75	4.0 ± 0.2	3215 ± 199
B. Vitamin A Incision/Fracture		688 ± 36 ^a	2254 ± 82	3.5 ± 0.2 ^c	3315 ± 140 ^d
C. Peanut Oil Incision	14 Days Postop	671 ± 47	2273 ± 91	3.9 ± 0.3	2923 ± 116
D. Vitamin A Incision		866 ± 35 ^b	2440 ± 106	3.0 ± 0.2 ^c	3004 ± 124

^aSignificantly increased over fracture rats given peanut oil (P<0.02).

^bSignificantly increased over fracture rats given vitamin A and over peanut oil groups (P<0.001).

^cSignificantly lower than peanut oil group (P<0.02).

^dSignificantly increased over wounded rats given vitamin A (P = 0.02).

TABLE 4. Body Weights and Food Intakes of Injured Rats, Some Given Oral and Topical Vitamin A

Experiment 2 Ad libitum Fed							
Group			Wt, gm†	Days	Postop. Intake*		Cals
					Food	Prot	
A ₂	Peanut oil	Operated	357 ± 2	2	4.0	1.0	14
	Incision/Fracture	Sacrificed	371 ± 4	11	6.9	1.7	23
B ₂	Vitamin A	Operated	365 ± 2	2	4.8	1.2	16
	Incision/Fracture	Sacrificed	380 ± 3	11	7.2	1.8	25
C ₂	Peanut oil	Operated	364 ± 2	2	4.5	1.1	15
	Incision/Fracture	Sacrificed	371 ± 3	10	6.9	1.7	24
D ₂	Vitamin A	Operated	361 ± 2	2	4.7	1.2	16
	Incision/Fracture	Sacrificed	369 ± 3	10	7.2§	1.8	25

*Average food intake (gm/100 gm body wt) for first two days and entire postoperative period. Protein (gm/100 gm body wt) equals TN determined by micro-Kjeldahl × 6.25. Calories/100 gm body wt estimated from manufacturer's ration composition. †Mean ± S.E. §Ad libitum fed rats given vitamin A ate more food than rats given peanut oil ($P = 0.05$) in 10 day study.

Experiment 2

Ad libitum fed rats with fracture given peanut oil (groups A₂ and C₂) or vitamin A (groups B₂ and D₂) lost about 5% of their body weight the first two days after injury. By the sixth postoperative day, all the rats had begun to gain weight and when sacrificed, the vitamin A groups had regained only one more gram than the peanut oil groups as compared with their weights at operation. The vitamin A and peanut oil groups had a reduced food intake of 35 and 38% respectively during the first two postoperative days (Table 4). Food intake reached preoperative levels after 6 days matching preoperative intakes the remaining postoperative period. When the postoperative food and nutrient intakes of the ad libitum fed rat groups were compared, the vitamin A groups ate slightly more (4%) than the peanut oil groups.

When tested for breaking strength, skin wounds of rats given vitamin A compared with peanut oil groups were found significantly stronger (31%, $P = 0.01$) at 11 days

postoperatively. The hydroxyproline contents of the sponge granulomas of the vitamin A groups were higher than for the peanut oil groups (49%, $P = 0.01$). The hydroxyproline contents of sponge-induced granulomas were also significantly higher (36%, $P = 0.01$) for the vitamin A group at 10 days postoperatively but the wound strengths were not significantly different in the two groups of rats.

Liver vitamin A was significantly increased (5-14 fold) among animals given vitamin A as compared with those given peanut oil ($P < 0.001$). No differences in serum vitamin A concentrations were found among the vitamin A and peanut oil groups (Table 6).

For histologic evaluation of the skin incisions and sponge granulomas of the rats sacrificed at 11 days, a quantitation for each category described was based on arbitrary scales of 1 to 3 and the ratios of ground substance to collagen calculated (Table 7). No statistically significant differences in collagen and ground substance were found by the examination of skin wounds. Ground

TABLE 5. Wound Strength and Sponge Granuloma Hydroxyproline of Injured Rats Given Oral and Topical Vitamin A: (Mean ± S. E.)

Experiment 2: Ad libitum fed					
Group		Fresh	Breaking Strength, gm Formalin	<u>Formalin</u> Fresh	OHP μg/100 mg sponge)
11 Days Postop					
A ₂	Peanut Oil Incision/Fracture	461 ± 21	1594 ± 59	3.7 ± 0.2	1993 ± 45
B ₂	Vitamin A Incision/Fracture	606 ± 36*	1838 ± 63*	3.3 ± 0.2	2975 ± 158*
10 Days Postop					
C ₂	Peanut Oil Incision/Fracture	410 ± 27	1230 ± 52	3.3 ± 0.2	1864 ± 107
D ₂	Vitamin A Incision/Fracture	399 ± 26	1276 ± 49	3.5 ± 0.2	2524 ± 134*

*Significantly increased over peanut oil group ($P = 0.01$)

TABLE 6. Liver and Serum Vitamin A Levels of Injured *Ad libitum* Fed Rats Given Oral and Topical Peanut Oil or Vitamin A: (12 Rats/Group)

11 Days Postoperatively						
Group*	Liver Wt, gm		Liver Vit. A	µg/Gm	µg	Serum Vit. A µg/100 ml
	Wet	Per Kg Body Wt				
Peanut Oil	12.8 ± 0.5	34.6 ± 1.2	Dry	20 ± 1	70 ± 5	62 ± 3
Vitamin A	12.7 ± 0.3	33.3 ± 0.6	3.6 ± 0.1	100 ± 19†	372 ± 78†	69 ± 2
10 Days Postoperatively						
Peanut Oil	11.9 ± 0.3	32.1 ± 0.6	3.4 ± 0.1	17 ± 1	57 ± 5	73 ± 4
Vitamin A	12.2 ± 0.3	32.8 ± 0.6	3.6 ± 0.1	231 ± 14†	835 ± 47†	64 ± 3

(Mean ± S. E.)

*With skin incision and unilateral femoral fracture.

†Significantly increased over peanut oil group ($P < 0.001$).

substance of sponge granulomas of vitamin A fractured rats compared with the peanut oil group was significantly increased ($P = 0.02$) as was the ratio of ground substance to collagen ($P = 0.001$) at 11 days postoperative. No differences were apparent in the numbers of fibroblasts in the wounds or sponge granulomas of the peanut oil and vitamin A groups.

Discussion

At present the physiological action of vitamin A in wound healing remains unclear, but some previous studies have been made on the relationships between vitamin A and the biological control of wound healing.¹⁷ The protective effect of the vitamin in reversing the inhibitory effect of anti-inflammatory steroids such as cortisone⁸ and other anti-inflammatory agents⁹ such as aspirin has attracted a great deal of attention. In this regard Howes et al.⁶ reporting on the retardation of wound healing by cortisone observed that a hormone-like substance which can completely stop such profound defense

mechanisms as the sprouting of new blood vessels and fibroplasia is not only significant in itself, but conversely, the finding suggests that an offsetting mechanism must likewise exist whenever a wound heals.

There is now general agreement that vitamin A has hormone-like properties and yet functions as a vitamin.²⁰ Ehrlich and Hunt³ have shown that vitamin A overcame this inhibitory effect of cortisone on the rate of gain in tensile strength in early stages of healing of primarily closed wounds in rats, yet vitamin A alone had no effect on wound healing in normal animals. Hunt *et al.*⁸ later reported that vitamin A stimulated healing of cortisone-retarded open wounds in rabbits and had some benefit in the healing of open wounds in some patients. In these experiments vitamin A again did not significantly enhance healing beyond the normal rate when cortisone was not given. Lee and Tong⁹ also demonstrated that the healing retardation of salicylates, hydrocortisone and prednisone can be reversed by applying retinoic acid on the wound. Recently, Chernov et al.² reported that the administration of vitamin A reduces the risk of stress ulcers in severely stressed patients.

The rats in the studies reported in this paper were nourished normally up to operation and injury, and supplemental oral and topical vitamin A treatments were initiated postoperatively. This is in contrast to an earlier study⁴ in our laboratory on the influence of vitamin A on wound healing in which the rats were deprived of vitamin A for varying periods preoperatively, as well as postoperatively. Vitamin A deficient rats had slower growth rates, weaker wounds, made less sponge granuloma reparative tissue than control rats, the reparative wound collagen was less cross-linked, and many died.

Our arbitrary choice to allow the group of rats with fracture given peanut oil in the first experiment to select their food voluntarily and then to give the same food allowances to their pairs in the other groups resulted in slightly lower (3-5%) food intakes for vitamin A treated animals with and without fracture. These latter groups of rats nevertheless gained more weight postoperatively than the rats with higher food intakes given peanut oil. In the second experiment in which all rats ate *ad libitum*, there was no apparent effect of vitamin A on food intake or body weight.

TABLE 7. Comparison of the Histologic Evaluation of Wound Healing, Skin Incision Breaking Strength and Sponge Granuloma Hydroxyproline Content of Rats at 11 Days Postoper.

Group	A—Peanut Oil Unilateral	B—Vitamin A Unilateral
Femoral Fracture		
<i>Skin Incision</i>		
Collagen (Coll)	1.6 ± 0.1	1.4 ± 0.1
Ground Substance (G S)	1.3 ± 0.2	1.3 ± 0.2
Ratio — Coll	0.88 ± 0.09	1.03 ± 0.18
No. Fibroblasts	1.1 ± 0.1	1.1 ± 0.1
Breaking Strength	461 ± 21	606 ± 36†
<i>Sponge Granuloma</i>		
Collagen (Coll)	2.5 ± 0.1	2.1 ± 0.2
Ground Substance (G S)	1.1 ± 0.1	1.5 ± 0.2*
Ratio — Coll	0.44 ± 0.03	0.74 ± 0.08§
No. Fibroblasts	2.2 ± 0.1	2.3 ± 0.2
Hydroxyproline	1993 ± 45	2975 ± 58†

(Mean ± S. E.)

Significantly increased over peanut oil group * $P = 0.02$; † $P = 0.01$; § $P = 0.001$

In our experiments, after 2 weeks, oral vitamin A and the topical application of vitamin A to the skin incisions resulted in improved wound healing among rats with skin incisions only and also among rats with skin incisions and femoral fracture after 11 days (but not in the 10 day group) compared with similar rats given peanut oil. The lower formalin fixed: fresh breaking strength ratios found in experiment 1 for the vitamin A treated rats suggest the presence of greater cross-linking of reparative collagen in the wounds of rats given vitamin A. The increased hydroxyproline content of the granulomas of *ad libitum* fed rats in experiment 2 given vitamin A, particularly rats with fractures, indicates increased reparative collagen formation under the influence of vitamin A. This was supported by the histological appearance, i.e., slightly more collagen and a significantly lower ratio of G.S.: collagen of the sponge granulomas. Our findings are in agreement with those of Herrmann and Woodward⁵ who reported an increase in tissue ingrowth and collagen formation into PVA sponge implants and a concomitant increase in wound strength in rats with dorsal skin incisions given local and systemic vitamin A.

These findings are at variance with those of Ehrlich and Hunt who reported that vitamin A, 1500 I.U. (0.5 mg) in peanut oil given intraperitoneally on the day of wounding, two and four days later had no effect on the breaking strength of dorsal incisions measured two days after the last vitamin A injection. Their controls received no injections. Our studies were undertaken with rats of the same strain and sex as those of Ehrlich and Hunt. In both cases, the rats were housed individually and ingested a commercial rat chow, but from different suppliers. In our experiments, oral (1 mg) and topical (2 mg) vitamin A were given for one week starting right after operation and the wound healing was evaluated 10-14 days postoperatively.

Summary

Oral and topical vitamin A given to rats with a skin wound with and without femoral fracture resulted in increased wound strength in pair-fed rats and *ad libitum* fed rats as compared to controls given peanut oil. Increased tissue ingrowth and collagen formation in sponge granuloma were found for *ad libitum* fed rats with fracture given vitamin A but was unchanged among pair-fed wounded rats with and without fracture. Histologic examination of the skin wound and sponge granuloma showed increased fibroplasia and collagen elaboration in

ad libitum fed rats given vitamin A compared with similar rats given peanut oil.

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Wound Healing in Man:

Tensile Strength of Healing Wounds in Some Patient Groups

ERIC LINDSTEDT AND PHILIP SANDBLOM

The healing of test wounds was studied in 108 patients, in whom some impairment of wound healing was suspected. A 5 cm skin wound was performed in the forearm and the strength of the wound was tested after 5 days using the technique described by Sandblom and associates with two measurements in each wound. No differences in wound strength could be registered between the two wounds in each patient, between males and females nor in patients with malignant disease compared to other patients. Patients with low serum protein or serum albumin values had significantly weaker wounds than patients with normal protein values. Patients over 80 years of age had wounds somewhat weaker than those below 70, the difference having a statistical significance of 6%. The wound strength in patients was compared to values found elsewhere for wounds in rabbits, rats, and piglets. The pigs had much higher values than others, rabbits slightly stronger than and rats about equal to humans.

OUR KNOWLEDGE about the wound healing mechanism in man is still incomplete. Valuable information has been obtained by comparing results from animal experiments with clinical observations of human wound healing after operation and trauma. Many similarities exist in the course of healing of connective tissue in different species of animals.^{6,10} It is not, however, possible to transfer completely the information from animal experiments to clinical conditions. There are many differences between research animals and man regarding the anatomy of the skin and the histological appearance of the wound healing process.⁸

Relatively few wound healing studies have been performed in man. Du Noüy⁵ measured the rate of healing of skin defects and could demonstrate that young patients healed faster than old. Baxter et al.¹ studied biopsies

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from patients given adrenocorticotrophic hormones and could demonstrate decreased rate of healing in some cases. Wolfer et al.²⁸ measured the tensile strength of excised wounds of the skin and the fascia lata in volunteers deficient in Vitamin C.

By measuring the rate of decrease of the volume of the wound cavity after excision of pilonidal cysts the importance of zinc for wound healing in man was studied.¹⁹ The incorporation of ³⁵S-cystein in the wound area⁷ and chemical and metabolic factors concerning the ground substance¹⁴ have been studied. The role of oxygen content and oxygen consumption in the wound¹¹ has also been studied in man.

Prior knowledge of the wound healing capacity in patients with special types of disease is of great importance in the selection of an appropriate treatment and for the prognosis of the patient. In order to study the strength of healing wounds in such patients, it was necessary to devise a technique where the tensile strength of a wound could be measured in situ, giving as little discomfort as possible to the patient. Such measurements of the tensile strength of wounds in patients was made possible by the technique described by Sandblom et al.²⁵ and preliminary results were described by these authors and by Olsson.¹⁸

We have made further studies using this technique. Our aim was to study the accuracy of the technique and its usefulness in detecting differences in the wound healing capacity of various patient groups. We especially studied the effect of sex, age, serum protein levels and malignant disease and compared our results in humans with previous findings in various species of animals.

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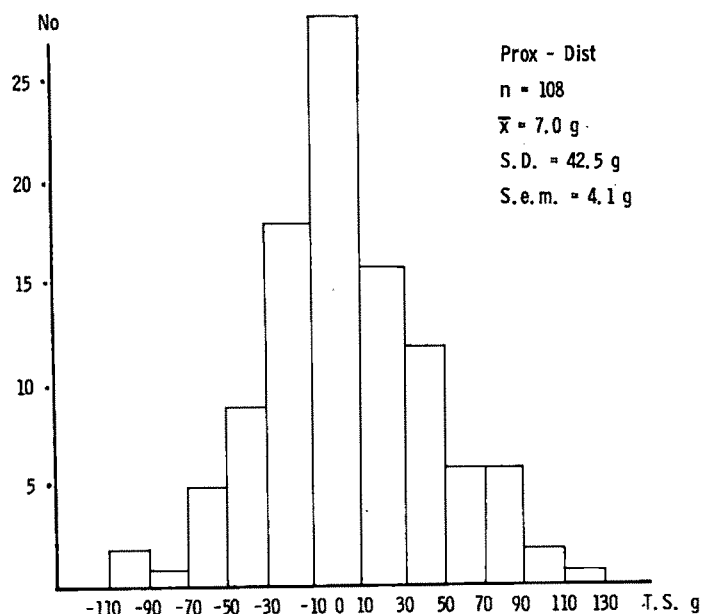


FIG. 1. Distribution of the difference (Prox—Dist) of the two observations in each patient.

Material and Methods

One hundred eight patients, 61 males and 47 females, were studied. They were admitted to the hospital for surgical evaluation, and in most cases major operations were planned. In every one there was a suspicion that wound healing might be impaired. There was thus ample reason for subjecting the patient to the small inconvenience that the examination incurred. All studies were performed with the informed consent of the patients. The patients were anesthetised using trichlorethylene (Trilene®) administered by a special inhalation apparatus.

A 5 cm longitudinal incision wound was made through the skin on the volar side of the forearm a few cm below the elbow. Cutting of subcutaneous veins was avoided. By light compression of the wound haemostasis was achieved without using ligatures. The wound was closed by isolated sutures of 4/0 silk, 5 mm apart. The strength of the wound was tested after exactly 5 days. For local anaesthesia 0.5% mepivacaine (Carbocain®) without adrenaline was infiltrated around the wound. The sutures, except for one in the middle of the wound, were removed. The wound was tested in two places by the technique described by Sandblom et al.^{25,26} using the modified tensiometer used by Sandberg.²¹ The result was given as bursting force in grams. For some calculations both the proximal (Prox) and distal (Dist) observations were used. For most calculations the mean value of the two observations in each patient ($\frac{\text{Prox} + \text{Dist}}{2}$) was used.

In most cases serum protein content was measured in venous blood drawn in the morning from the fasting patient. Total protein was determined by a Kjeldahl

method and the albumin level calculated from serum paper electrophoresis. The Student's *t*-test was used for a statistical analysis in most situations, otherwise the Wilcoxon two-sample test was used.

Results

The dispersion of the values for the two wounds tested in each patient is illustrated in Fig. 1. Seventeen patients had the same value for the two observations and in another ten the difference was less than 10 g. Among the remaining 91 a difference of up to 120 g was found. There was no statistically significant difference between the strength of the proximal and the distal wounds (mean = 7.04 g, SD = 42.5, sem = 4.1).

To study the accuracy of the testing method the standard deviation of the mean values of the two observations in the 108 patients (mean = 181.5 g, SD = 50.92, sem = 4.9) and for the differences between the two observations (see above) were compared. The variance ratio is $\frac{50.9^2}{42.5^2} = 1.43$ which is significant ($0.05 > P > 0.01$). We thus accept the method as being accurate enough for detecting significant differences in a reasonably small sample of patients.

In order to find out how many observations would be necessary to detect a given difference in the mean value, we collected 53 patients, who could be supposed to have a wound healing capacity as close to "normal" as possible. That means that they were below 70 years, had normal serum albumin levels and no known malignant disease. These patients had a mean value of 189.8 g, SD = 46.6 g. We made the further assumptions:

1. One-sided *t*-test is used for calculation of significance. The desired level of significance is 2.5%.
2. The standard deviation in the new sample should be fixed beforehand and be of the same magnitude as in the reference sample of 53 patients.
3. The observations must correspond reasonably well to a normal distribution.

Under the given conditions, we found that a difference of 10% between the mean values could be detected in a new sample of 39 patients, and that increasing the number of observations above this adds very little to our chance to detect a difference. If the difference is as large as 15% it will be detected even in a sample of 20 patients. If the series is limited to 10 patients the difference must be at least 20% in order to be detected with significance. The distribution of the mean values for each patient is illustrated in Fig. 2. The range of the wound strength, measured is 78 to 340 g.

The comparison between females and males is shown in Fig. 3. The mean value for the 47 women was 174.5 ± 7.9 g (sem), and for the 61 men, 187.2 ± 6.0 g. There is thus no significant difference between females and males.

We compared the values for patients having serum

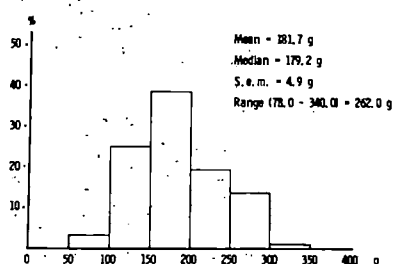


FIG. 2. Frequency diagram (%) for the frequencies of the mean values (Prox + Dist/2) for 108 patients.

albumin values less than 3.5 g per 100 ml or total serum protein less than 6.5 g per 100 ml to patients with higher serum albumin or serum protein levels (Fig. 4). The mean value for patients with higher protein values is significantly higher than that of patients with lower protein values ($P = 0.025$).

The wound strength has been plotted against patient age. There is a slight tendency towards lower values in older patients but the correlation is far from being statistically significant. As we found the serum protein value to be important for wound strength we excluded patients having serum albumin values below 3.5 g per 100 ml or total serum protein below 6.5 g per 100 ml in order to get patient groups as close to normal as possible. We collected one group of patients above 80 years of age and another group below 70 (Fig. 5). Seventeen patients over 80 had a mean value of 169.8 ± 9.1 g (sem) while 32 patients below 70 had 189.5 ± 8.3 g. Using the *t*-test in comparing these values we found *P* lying between 5 and 10%. Using the Wilcoxon two-sample-test, one-sided test, *P* was found to be below 0.06. The wound strength for these patients over 80 are thus close to being significantly lower than for patients below 70.

For practical reasons we have not yet sufficient results to evaluate wound healing capacity in infants.

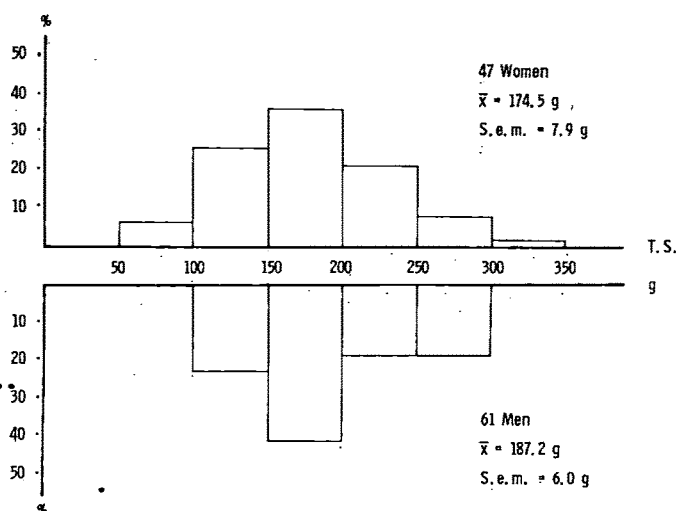


FIG. 3. Frequency diagrams for the 47 women compared to the 61 men. No significant difference.

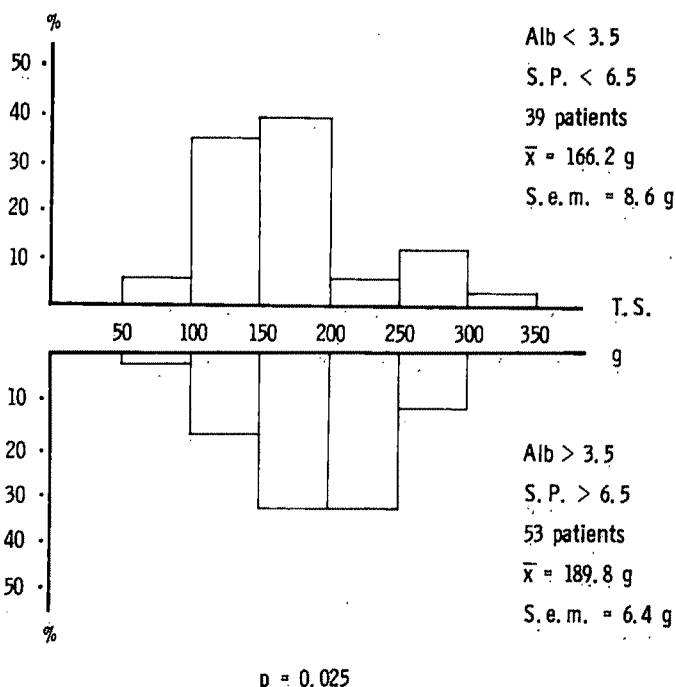


FIG. 4. Frequency diagram for patients with low serum protein values compared to patients with normal protein values. The patients with normal protein values have significantly stronger wounds.

Patients having malignant disease were compared to patients without malignant disease. No significant difference could be found. Not even patients with malignant disease of the gastrointestinal tract, (cancer of the stomach, of the colon or of the rectum) had wound strength significantly lower than other patients.

Sandblom²⁴ compared the mean values for 5 patients having Cushing's disease to the mean values of the whole material at that time (Fig. 6). In one case with pronounced Cushing's syndrome caused by adrenal cortex tumor the tensile strength was excessively low before operation and returned to normal shortly thereafter (Fig. 7).

Wound Strength in Various Species of Animals

Zederfeldt²⁹ found the strength of 5-day wounds in rabbits to be 276.2 ± 7.2 which is somewhat higher than in our patients.

Sandberg and Zederfeldt²² compared the strength of wounds in rabbits and in rats. They found the wounds to be somewhat weaker in rats. This means that the strength of wounds in rats are of the same magnitude as in our patients.

Lindstedt¹⁵ made wound healing studies in piglets weighing 7-19 kg but made the wounds only 1.5 or 2 cm in length. The wounds were tested with the same tensiometer but special claws were constructed to test these small wounds. In 24 wounds tested on day 5, the strength was 324 ± 7.2 g. In 9 patients, three 1.5 cm wounds were made in the forearm in each patient and tested on day 5

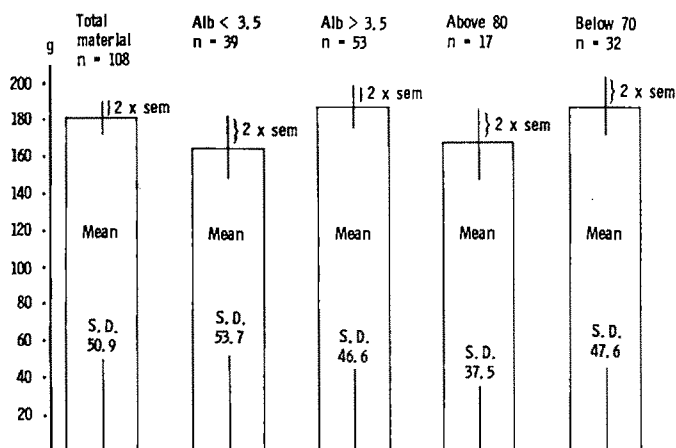


FIG. 5. Collective diagram for the total material, and for the groups where differences can be registered.

using exactly the same technique as in the pig. These small wounds had a strength of 110 ± 4.8 g. It thus seems that the wound strength on the fifth post-wounding day is considerably stronger in the pig than in humans.

From what is quoted above, it would seem that the pig gives the strongest wounds, rabbits slightly stronger than humans, rats and humans about equal. No consideration is taken as to skin thickness.

Discussion

For statistical analyses in this investigation, the Student's *t*-test was used in most situations. When the results using this seemed questionable, we applied the Wilcoxon test. The assumption underlying the *t*-test is that of two normal distributions with equal standard deviations. No medical data follow a normal distribution—however, good approximations often occur, and the *t*-test is widely used. The Wilcoxon test on the other hand makes no assumption of "normality." The only assumption underlying the Wilcoxon test is that the data follow a completely general continuous distribution. This latter assumption is almost always fulfilled when the *t*-test is

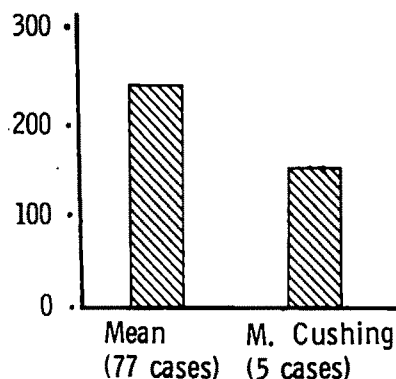


FIG. 6. Tensile strength values for 5 patients with Cushing's disease compared to the total material at that time (Sandblom, 1957²⁴).

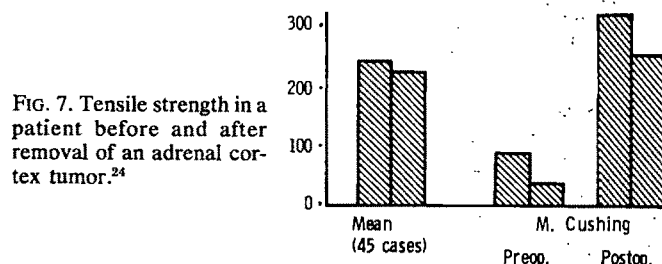


FIG. 7. Tensile strength in a patient before and after removal of an adrenal cortex tumor.²⁴

appropriate. Therefore, one should rely more upon the Wilcoxon testing procedure and the related *P*-value than upon the corresponding inference arising from the *t*-test.

There is a fairly wide variance for the two observations in each patient. Some of the differences between the two wounds may be due to technical errors in performing the wounds and in the technique of testing.

As the variance of the difference between the two values for each patient is significantly lower than the variance for the different patients, the method should be worth using. The method was accurate enough to show significant difference between the plasma protein groups and borderline significance in the age groups.

Many factors may affect a study of this kind in patients. Thus, the technique was standardized as far as possible. As local infiltration anesthesia might affect wound healing,¹⁷ this was avoided. Trichlorethylene analgesia, as used in this study, is rather innocent and gives no untoward effects upon the patients. In patients with cardiac arrhythmias, wound healing studies were avoided. The interval for wound testing, 5 days, was chosen because this time was found to be suitable in animal experiments,²³ and because it was desirable to choose as short time as possible to avoid delay of the adequate treatment of the patients' disease.

The investigation does not represent a normal material, as in every patient there was a suspicion of a delay in wound healing. Therefore the normal healing is probably somewhat higher than shown in this material.

No differences between the sexes could be found, and this is in accordance with experiences from animal experiments.

The effect of hypoproteinemia on wound healing is known from animal experiments²⁷ and protein deficiency has been found in half of patients with disrupted abdominal wounds.¹⁶ Koster and Shapiro¹² found serum albumin values below 3.75 g per 100 ml in 86% of patients with wound healing complications, while 20% of patients with normal wound healing had the same degree of protein deficiency. In experimentally created protein deficiency in dogs, decreased wound healing capacity was found histologically.²⁰ The wound healing capacity could be normalized by administration of a colloid solution. The decreased wound healing capacity found in our patients with hypoproteinemia is thus not unexpected.

Many of these patients have other important disease factors of which the decreased serum albumin value may be one indication. The low wound strength in patients with protein-losing non-malignant intestinal diseases point to the importance of isolated serum albumin deficiency. The importance of advanced age for the healing of wounds is debatable. In lower animals, decreased wound healing capacity with increased age has been found, but the conditions are more complex in mammals.⁴ Bourliere² found a higher rate of healing in young than in middle-aged rats. In the very old rats the wound healing has been found to be as good as in the middle-age group.^{2,9} Leaming¹³ showed that different age groups of rats had the same wound strength up to 5 days but after this time the older rats had a stronger wound, probably due to the greater strength of normal skin in the older rats. By studying the wound healing of skin defects in war injuries, faster healing was demonstrated in young patients.⁵ In the present material, the lower wound strength in the older age group could be due to age itself. It could, however, also be due to other diseases in these patients, atherosclerosis, diabetes, malignant disease or deficient diet including lack of vitamins and protein. The tissue atrophy giving a thin dermis with low normal strength in many old patients has probably little influence on wound strength after 5 days. Our results point to the importance of special care concerning adequate nutrition and wound care in old patients. It is, however, apparent that many of the very old patients have a completely normal wound strength. As has been pointed out^{3,24} there is no reason to avoid necessary surgical procedures in even very old patients because of the risk of inadequate wound healing.

The low wound strength of some patients with Cushing's disease is of great theoretical interest. The number of patients is, however, too small to allow statistical analysis.

The presence of a malignant disease does not in itself necessarily mean any decrease in the capacity of wound healing. Significantly lower wound strength could not even be demonstrated in patients with malignant disease of the digestive tract. Very low values in some of these patients could probably be explained by protein deficiency.

The relative strength of wounds in different species of animals is of some theoretical interest. The small differences between man, rat and rabbit is remarkable. The considerably higher values for piglets is also interesting. The much higher thickness and toughness of the pig skin and the fact that these animals were young (8-16 weeks) and growing very rapidly, may be contributing factors.

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The Hepatorenal Syndrome: Recovery After Portacaval Shunt

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Reversal of the morbid hepato-renal syndrome has been achieved in a cirrhotic patient with ascites following successful side-to-side portacaval shunt. The hepatorenal syndrome is defined as progressive unresponsive renal failure with previously normal kidneys in the presence of impaired hepatic function. Although the etiologic mechanism has not been defined, it is suggested the relationship of increased intrahepatic sinusoidal pressure on the thoracic duct and subsequent decreased lymph flow are inter-related to increased levels of aldosterone and manifested by (chylous) ascites. Laboratory and clinical evidence suggest that cirrhotics with ascites have remarkably high levels of aldosterone secretion via the rennin-angiotensin-adrenal cortex mechanism. This is the group that develops hepatorenal syndrome. Reduction of the intrahepatic pressure and decompression of the portal hypertension can be successfully achieved with a side-to-side shunt which should return the aldosterone-rennin-angiotensin axis to normal and subsequently reverse the hepatorenal syndrome.

PROGRESSIVE renal failure in the presence of impaired hepatic function has been described in a variety of disorders grouped as the "hepatorenal syndrome." The features of the hepatorenal syndrome (HRS) include azotemia, oliguria, and intense sodium retention in the presence of histologically normal kidneys.

Classically the HRS occurs in cirrhotics in whom there is no evidence of pre-existing renal disease. Hecker and Sherlock reported 9 cirrhotic patients who died in renal failure.⁷ Papper and his associates reported an additional 22 patients with HRS—all of whom died.¹⁵ Various attempts at treating this condition have been unsuccessful, and the HRS is usually a terminal event.^{2,17,18}

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Case Report

This was the second admission to the West Haven Veterans Administration Hospital for this 78-year-old Caucasian man with cirrhosis of unknown etiology. He was in good health until mid-1971 when he experienced insidious onset of ascites with no history of alcohol ingestion or hepatitis. A liver biopsy on that admission was read as mild inflammatory changes. The ascites was controlled with diuretics, and the patient was discharged.

He did well until December, 1973, when he had an episode of hematemesis and bright red blood per rectum. On admission to another hospital, Hct. was 20%. Esophagoscopy showed 4+ varices without an obvious bleeding point. He required a 13 unit blood replacement after which he had an episode of hepatic coma controlled with neomycin. The ascites flared, and he required treatment with diuretics.

On admission to the West Haven V.A. Hospital, he was noted to have tense ascites with 4+ pitting edema of lower extremities. HAA was negative. A liver scan showed a small liver with enlarged spleen. He was placed on Aldactone, Digitoxin, low salt and protein diet and fluid restriction. Repeat liver biopsy showed fibrosis of the portal tracts. After several weeks, the ascites improved significantly, and he was discharged.

One week prior to the second admission at this hospital, he noticed increasing ascites and 7 lb. weight gain. Paracentesis on this admission revealed chylous ascites with 355 mg.% lipids. Attempts at diuresis resulted in a rise in the BUN from 33 to 51. It was also noted that he had an enlarging umbilical hernia which was beginning to ulcerate.

Femoral cath studies revealed a hepatic wedge pres-

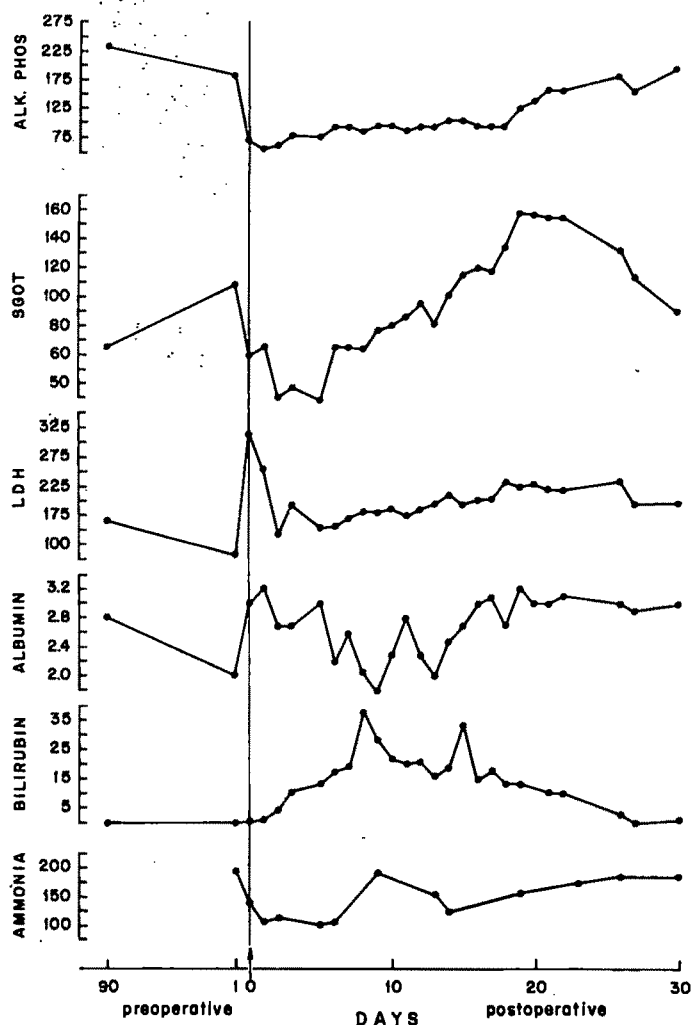


FIG. 1A. Laboratory studies pre and post side-to-side portacaval shunt.

sure of 32 mm Hg.; the IVC was within normal limits and no hepatofugal flow. Attempts were made to reduce the ascites with serial paracenteses and plasma expanders, but his BUN continued to rise, and serum albumin went down. It was decided that a side-to-side portacaval shunt should be performed in light of intractable ascites, ulcerating umbilical hernia and progressive hepatorenal syndrome.

Just prior to surgery, an SMA catheter was placed and the venous anatomy outlined. This also served as a means of vasopressin infusion at time of surgery if needed.

A successful side-to-side shunt was performed. Postoperatively, the HRS was relieved (Figs. 1 A and B).

Discussion

Spontaneous recovery from the HRS is indeed rare. Although Galambos and Wilkinson described the first recovery of a patient with hyponatremia, they never con-

sidered the patient to have HRS.⁵ Baldus and his associates reported recovery in 6 of their 25 patients with HRS.² However, the azotemia was present for less than 3 weeks in these patients. Goldstein and Boyle reported 4 additional cases of survivors from this syndrome.⁶ In all these reports, recovery could be correlated with improvement in hepatic function. This is further evidence that the kidneys are structurally normal. It has also been shown that kidneys from patients who have died from the HRS function normally when transplanted into patients with chronic uremia.⁸

One feature remains prominent in the review of HRS; the presence of ascites.^{2,5,17,18} In fact, it may be the *sine qua non* of the HRS.⁴ There is evidence to suggest that cirrhotics with ascites have abnormally high aldosterone secretion,¹ and that this hyperaldosteronism is responsible for the marked salt and water retention. Although the cause of the hyperaldosteronism is not known, patients with cirrhosis but no ascites do not secrete high levels of aldosterone.¹⁹

In a series of laboratory studies on dogs, Orloff and his associates investigated the relationship between ascites and aldosterone secretion. Increased intrahepatic pressure from minimal hepatic outflow occlusion resulted in

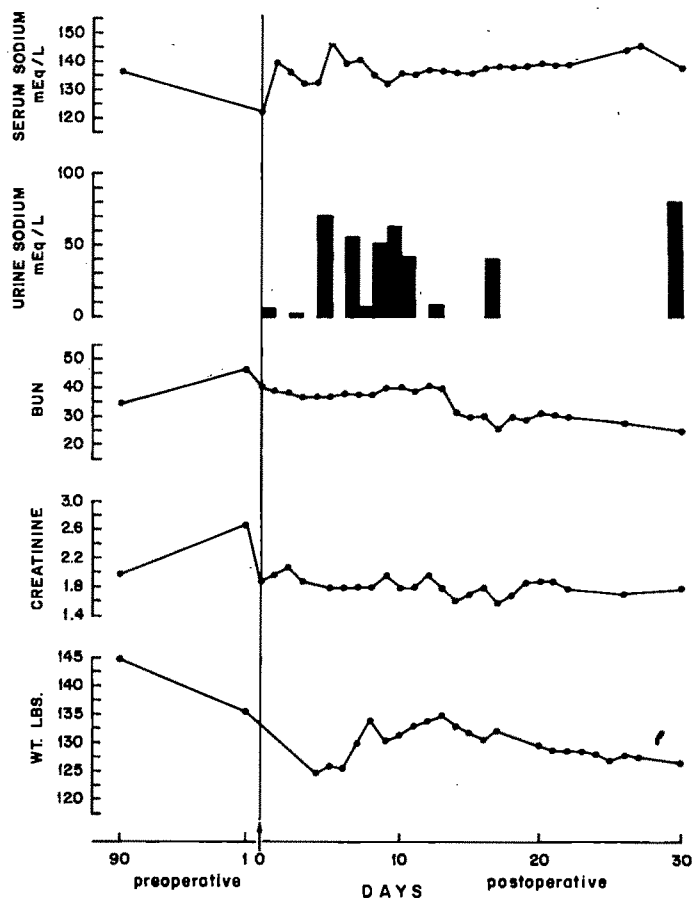


FIG. 1B. Laboratory studies pre and post side-to-side portacaval shunt.

prompt 4-to-5 fold increase in aldosterone secretion,¹³ which was abolished in nephrectomized dogs,¹⁰ and again increased in normal dogs cross-transfused with blood from nephrectomized dogs undergoing minimal hepatic outflow occlusion.¹² They proposed that intrahepatic hypertension played a role in the hyperaldosteronism associated with cirrhotic ascites, presumably through a renin-angiotensin pathway with the adrenal cortex.

Further laboratory studies demonstrated that side-to-side portacaval shunts in dogs were significantly better than end-to-side shunts in relieving well-established persistent ascites,¹⁴ decompressing liver sinusoidal and thoracic duct pressures,¹¹ as well as decreasing aldosterone secretion.¹⁰

On the basis of these experimental observations, 9 patients with intractable ascites and hyperaldosteronism were treated with side-to-side portacaval shunts with resolution of the ascites, decrease in aldosterone secretion, and increase in urine output.⁹ Wolfman and his associates,²⁰ and Burchell, et al.,³ demonstrated similar results in their experiences with side-to-side shunts.

Schroeder and his colleagues reported the first recovery from the HRS following a side-to-side portacaval shunt in a 42-year-old woman with intractable ascites and renal failure secondary to alcoholic cirrhosis.¹⁶ The hyperaldosteronism, renal dilution mechanism, and plasma renins returned to normal after the shunt.

Our patient is the second such case to recover from the HRS following a surgical procedure to decompress the portal venous hypertension.

It would seem reasonable from previous laboratory and clinical trials that a decompression procedure which would lower intrahepatic pressure would revert the aldosterone levels to normal, as well as alleviate the ascites. In our patient, the abdominal fluid was a chylous ascites. Orloff has shown that the intrahepatic sinusoidal pressure rise also increased the pressure of the thoracic duct and decreased lymphatic flow. In our case, this could be a reflection of actual contribution to the ascites from the thoracic duct or the bowel wall. For these reasons, a side-to-side shunt was used to decompress the portal hypertension to give the maximal and optimal results for the treatment of ascites, chylous fluid, and return the aldosterone and rennin-angiotensin mechanisms of the HRS to normal.

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Infected Arterial Grafts

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The case notes of 664 patients who underwent surgery and arterial grafting between the years of 1955 and 1973 at the University of Rochester Medical Center have been analyzed. There were 15 cases of infected grafts—a rate of 2.3%. The outcome of the infection was determined in 12 of these cases. Four patients had no surgical treatment and all 4 died. Three patients had simple ligations with excision and one died, one had an above knee amputation and one continues to have a draining sinus. Five patients had axillofemoral bypasses. Two died and three patients are alive and well. The role of prophylactic antibiotics is briefly discussed and the influence of possible etiological factors is also considered.

INFECTED ARTERIAL GRAFTS are an uncommon and extremely serious complication of aorto-iliac surgery. The incidence of infection has been reported in the range 1% to 6%.^{4,7-9,18} Opinion still varies regarding the use of prophylactic antibiotics in preventing infection and in the management of the graft once infection has occurred.

This report analyzes a retrospective survey of 664 cases of patients who underwent surgery with arterial prosthetic insertion between the years 1955 and 1973 at the University of Rochester Medical Center.

Material

Operations were performed because of occlusive arterial disease in 297 cases. Of these, 153 cases had an aortofemoral bypass, 43 had an aorto-iliac bypass and 101 had an iliofemoral bypass. Operations were performed because of aortic aneurysmal disease in 362 cases. Of these, 61 had an aortofemoral bypass and 301 an aorto-iliac bypass (Table 1). 54 of these bypasses were performed as emergency procedures and the rest were elective bypasses. The operations were performed by both the attending and the resident staff and followup was done on the patients every 6 months. The great majority of the grafts were woven or knitted Dacron in type. Early in the series a few nylon grafts were used.

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One way analysis of variance has been used to find a F ratio between groups being compared.

Results

In the 664 cases there were 15 cases of an infected graft—a rate of 2.3%. In 7 cases the infecting organisms were *Staphylococci* and in 5 of these cases it was on limb only of the graft which was involved. In 6 cases the infecting organisms were *E. coli* and in 4 cases it was the main body of the graft which was involved. There were two cases of *Klebsiella* infection, one involving the body and one involving a limb of a graft. *Pseudomonas* and *Streptococcus* was also cultured once each from the above cases. The outcome of infection was determined in 12 cases and 7 of these patients died.

Factors Affecting the Rate of Infection (Table 2)

Groin incision. There were 315 cases with a groin incision and 10 infected grafts in this group. There were 32 cases without a groin incision and three infected grafts in this group. It could not be determined whether there was a groin incision or not in 24 cases. This difference is not significant at 5% level of probability.

In the groin, if a swelling occurred which subsequently drained blood or serous fluid this was designated a groin complication. Of the 315 cases with a groin incision 29 had no groin complication and there were 6 infected grafts in this group. In the 22 cases who did have a groin complication there were four infected grafts and this is a significantly greater number than in the uncomplicated group at a 1% level of probability.

Prophylactic antibiotics: It is a policy at this institution to give all patients prophylactic antibiotics if an aortic prosthesis is to be inserted. Early in the series penicillin and streptomycin was the most popular combination of drugs but now keflin and kanamycin are nearly always

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TABLE 1. *Classification of Operations Performed*

Type of Operation	Reason for Operation	
	Occlusive arterial disease	Aortic aneurysm
Aorto-iliac bypass	43	301
Aortofemoral bypass	153	61
Iliofemoral bypass	101	—
Totals	297	362

used. Antibiotics are started prior to operation and continued for 5-7 days postoperatively. As this policy was not always followed early in the series, 44 patients did not receive prophylactic antibiotics and one prosthesis became infected. There were 510 patients to whom it is known prophylactic antibiotics were given. Eleven of these prostheses became infected. Although the infection rate of the two groups is the same it is not valid to compare them.

Emergency or elective case: In 314 cases of elective aneurysm surgery there were 5 infected prostheses. In 53 cases of emergency operation for aneurysm there were 4 infected prostheses. This is a significantly greater number at the 1% level of probability.

Management of Infected Grafts

No operative treatment. There were 4 cases and all died of septicemia at 15, 21, 22 days and 12 months after their respective operations. In these cases either the cause of illness was not recognized until portmortem examination or death occurred before operation could be undertaken.

Simple ligation and/or excision. Two patients had ligation and local excision of a limb of the prosthesis. This led to severe ischemic ulcers in one patient and above-knee amputation and death from septicemia in the other patient. One further patient had a simple ligation and drainage of one limb of an aorto-femoral bypass and continues to have a sinus with drainage.

Axillo-femoral bypass. Five patients had axillo-femoral bypasses. Two patients died—both during the course of staged procedures. One patient had a right axillofemoral bypass inserted to bypass an infected right limb of a graft and, while recovering from this and awaiting removal of the prosthesis, died with a massive hemorrhage from an aortoduodenal fistula.

The other patient had an axillofemoral graft inserted to bypass an infected left limb of an aortic graft and while recovering from this and awaiting removal of the graft, bled from the right limb of the aortic prosthesis requiring emergency operation with total removal of the graft and insertion of a right axillofemoral bypass. The patient developed acute tubular necrosis and died.

In the 3 surviving patients in this group one had the graft excised and bilateral axillofemorals inserted at the

same operation and the other two had staged procedures. They had an axillofemoral bypass on the side of an infected aortic prosthesis and excision of the infected limb at the first operation and then some weeks later they had an axillofemoral bypass on the opposite side and the remainder of the aortic prosthesis removed.

Discussion

Mortality. The extremely serious nature of an infected graft is attested to by the high reported mortality rates of 25% to 75%.^{4,7,8,15,16} The mortality rate in our series is of a similar large order with 7 deaths in 12 cases.

Groin incision. In this series a groin incision was associated with a larger number of infected grafts. In those patients with a groin incision there was a 3.2% incidence of infection and in those without a groin incision an 0.9% incidence of infection. Szilyagi et al.¹⁶ observed a 1.6% infection rate in patients with a groin incision as opposed to 0.7% infection rate in those without a groin incision in patients undergoing aorto-ilio-femoral surgery. Although these findings suggest that patients who have groin incisions are more apt to have infected grafts, the differences in both series are not significant at the 5% level of probability.

It may justifiably be argued that a retrospective analysis of uncontrolled groups is not a valid way of making judgements regarding infection. However, unlike a groin incision, statistical analysis at least reinforces what is suspected intuitively in the case of emergency procedures and also groin complications; (i.e. that infection is more common in emergency situations and also in cases where a complication develops in a groin wound). In emergency cases conditions are far from optimal and patients are usually sicker at the time of operation than in elective cases. In the case of groin complications the higher incidence of infection may be a cause or an effect.

Prophylactic antibiotics. This is a subject which seems governed as much by surgical fashion as scientific fact.

TABLE 2. *Factors Affecting Rate of Infection*

	Total number	No. with infection	Rate of infection
Groin Incision			
Present	315	10	— 3.2%
Absent	325	3	— 0.9%
Groin complication			
Present	22	4	— 18.2%
Absent	293	6	— 2.0%
Prophylactic Antibiotics			
Used	510	11	— 2.2%
Not used	44	1	— 2.3%
Type of Procedure			
Emergency Aneurysm	53	4	— 7.5%
Elective Aneurysm	314	5	— 1.6%

The rate of infection in our series in those cases in whom it was certain that prophylactic antibiotics had been used was 2.2% (11 infections in 510 cases).

It will be noted that this is at the low end of reported infection rates of 1% to 6%.^{4,7-9,16} In the two other large series reported infection rates were 1.32% in 1662 cases¹⁶ and 1.34% in 890 cases.⁷ Neither of these groups used prophylactic antibiotics. In spite of the low rates of infection both authors recommend prophylactic antibiotics for future use—Szilyagi and his group if the groin is to be incised and Fry et al. on the basis of work done in dogs.¹⁰

Therefore although there is no scientific evidence to support prophylactic antibiotics in patients (there is some evidence in laboratory created situations in dogs,^{6,10} most authorities continue to recommend prophylactic antibiotics when an aortic prosthesis is to be inserted.¹⁴

Management of the infected graft. There is no single agreed method in managing these cases although the introduction of alternative bypass routes has led to their increasing use with excision of the graft.

In 1959 Schramel et al.¹³ described ligation and local excision for an infected limb of a graft. In 1961 Blaisdell et al.¹ first described removal of an infected dacron graft with bypass from the thoracic aorta to the extremities. Then in 1963 Blaisdell and Hall² described the axillary-femoral bypass and Shaw and Baue¹⁵ described the obturator foramen bypass. Also in 1963 Carter et al.¹¹ described vigorous local treatment of infected limbs of grafts with excellent results.

If there is no evidence that the suture lines of the graft are infected (i.e. no bleeding) nor the pseudo-intima, (i.e. no thrombosis) then local treatment may still be appropriate.^{11,14,16} Leaving the main body and opposite limb of the graft in place and removing only the infected limb has also been carried out with successful results.^{4,5} However, the only certain way to know that infection will be eradicated is to totally remove the prosthesis. This can be done at one operation with the insertion of bilateral axillo-femorals preceding the removal of the prosthesis or it can be done as a staged procedure concentrating in the first operation on the infected side, (providing it is a limb and not the main body of the graft which is involved). The total excision of the prosthesis and other side axillofemoral graft can be carried out at a separate operation.

Improving results with the axillofemoral bypass procedure has led to it being more widely used and in this situation it is often the procedure of choice.^{11,12}

Conclusion

A series of 664 cases with 2.3% rate of infection of aorto-ilio-femoral grafts is presented. The high mortality of this complication underlines the necessity for prevention which explains why most authorities recommend prophylactic antibiotics, although there is no scientific evidence which shows that they lead to a lower rate of infection.

Conservative methods of management sometimes eradicate infection, but the only certain cure is obtained by removing the graft totally. The development and success of axillofemoral bypass technics has led to its use in the management of infected prostheses.

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pHisoHex[®] between contacts

Protects
every hand...
the more it's used

Protects
every hospital service...
the more hands
that use it

Unlike many other antibacterial skin cleansers, pHisoHex[®] creates a bacteriostatic film that reduces resident hand staph and other gram-positive bacteria to minute fractions of original levels after a few days of regular use. Thus, the pHisoHex hand is continuously protected—even between scrubs—through cumulative action when pHisoHex is used as directed. RINSE THOROUGHLY AFTER USE. pHisoHex should not be used on burned or denuded skin. See brief summary for full details of warnings, contraindications, instructions for use, patient selection, and supply.

Gets between staff and staph



contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxypolyoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterol 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.



pHisoHex[®]

sudsing antibacterial soapless skin cleanser

pHisoHex contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxypolyoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterol 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control. (See Warnings.)

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with

dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

pHisoHex SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene. Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only*. If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly with water.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or gastric lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

Winthrop Winthrop Laboratories
New York, N.Y. 10016

(1653)



See next page for summary
of prescribing information.

On the surgical service...

Clinical confidence earned through experience



Keflin® I.V.

sodium cephalothin

2 Gm.* in 100-ml. ampoule

The confidence
that comes with 10 years'
experience†

Experience with Keflin has established a record of clinical effectiveness in serious skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

*Equivalent to cephalothin.

†Keflin became available for clinical investigation early in 1962 and to the profession in 1964.

Brief Summary. Consult the package literature for prescribing information.

Indications: Keflin® (sodium cephalothin, Lilly) is indicated for the treatment of serious infections caused by susceptible strains of the designated micro-organisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported.

[020774S]



400402

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

Anaerobic GI flora— site specific

The gastrointestinal tract of man contains an abundance of microorganisms composed predominantly of anaerobic bacteria. The geographic location of these bacteria in the intestine may explain the different rates of infectious complications associated with injuries to different parts of the gastrointestinal tract. Soilage from the upper portion of the small bowel is usually associated with a lower rate of infection than from the lower small bowel and colon.

Intra-abdominal infections: Intra-abdominal infections may complicate penetrating abdominal wounds, particularly when the integrity of the bowel has been compromised. Such complications are frequently associated with trauma resulting from automobile accidents or criminal violence (such as gunshot wounds or stabbings). Anaerobic infections may occur as postsurgical complications. Peritonitis and abscess formation may cause particular problems. Intra-abdominal infections may also occur when bowel tissue becomes necrotic or nonviable as in cases of vascular compromise, embolic disease, obstruction, strangulation, toxic dilatation, and similar conditions characterized by tissue anoxia.

Appropriate therapy for the infectious complications is often a concern of many physicians.

...and how to manage them: The initiation of antibiotic therapy, particularly when peritonitis exists, may be a matter of immediate importance. In such emergency situations, the surgeon's selection of an antibiotic is frequently made on the basis of scant etiologic evidence. However, his knowledge of the specific normal flora in a given area of the bowel and how the flora can be altered by certain pathologic conditions will aid him greatly in his antibiotic selection.

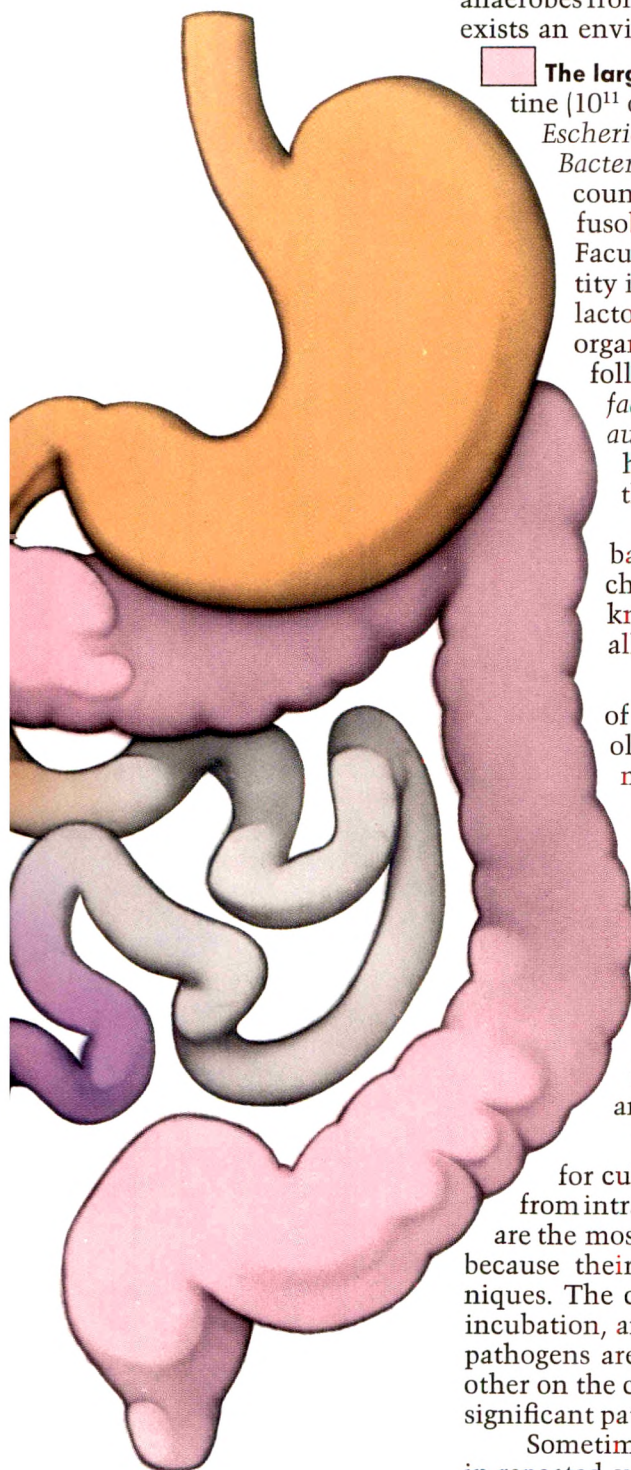
Therapy which must be initiated presumptively may be chosen discriminatively:

While inspection of Gram-stained specimens may prove useful, and cultures from the infection site will eventually provide valuable diagnostic information for the surgeon, the best clue to immediate antibiotic therapy may be the location of the infection. In the normal healthy adult, there is well-defined colonization by specific microorganisms in specific sites of the gastrointestinal tract. Thus a guide to the *normal* inhabitants of various areas may be helpful in suggesting the proper therapeutic agent.

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**Guide to the normal
adult intestinal
microflora**



The stomach, and proximal and middle small bowel: Here facultative enterococci, lactobacilli and anaerobes (originating in the oral cavity) exist in a concentration of 10^5 or less organisms per ml of contents. *Bacteroides fragilis* is virtually absent. Gastric acidity in this area limits the growth of many bacteria; therefore, most of the organisms are acid-resistant. In the middle portion of the small bowel there is sparse indigenous bacterial colonization, largely because of pronounced motility of this region.

The distal small bowel: In the ileum, enterococci and lactobacilli are seen in approximately the same quantities that occur in the stomach and duodenum. Coliforms are also observed—as are obligate anaerobes. *Bacteroides fragilis* and other fecal anaerobes first appear at this level. In fact, aerobic and anaerobic bacteria exist here in roughly equal proportions. The ileocecal valve, if functioning properly, provides a barrier against colonization by fecal anaerobes from the large bowel into this area. Beyond the ileocecal valve there exists an environment best suited to the proliferation of obligate anaerobes.

The large bowel: Anaerobic microorganisms predominate the large intestine (10^{11} organisms per gram of contents). Obligate anaerobes outnumber *Escherichia coli* 1,000 to 10,000 to one in the large intestine, and *Bacteroides fragilis* is the anaerobic organism most frequently encountered. Other anaerobes, such as peptostreptococci, clostridia, fusobacteria, and eubacteria are also seen although not so profusely. Facultative aerobes are in the decided minority here, but their quantity is no less than elsewhere in the intestinal tract. Enterococci and lactobacilli are each present in concentrations of about 10^6 to 10^8 organisms per gram of contents. *Escherichia coli* is most common, followed by enterococci (*Streptococcus faecalis* and *Streptococcus faecium*), proteus, pseudomonas, and klebsiella. *Staphylococcus aureus* and *Candida albicans* are also present in the large bowel of healthy, normal individuals. The pathogenic potential of each of these microorganisms should never be overlooked.

Because the large bowel contains many different species of bacteria, disease or trauma in this area may present a special challenge. Accordingly, it is important to remember that no known single agent has proved to be uniformly effective against all of these organisms.

Variations in the normal microflora: The normal microflora of the intestinal tract may be substantially altered in certain pathological conditions. These alterations depend upon the patient's medical history and the nature of his present illness. If, for example, the patient has achlorhydria, tissue ischemia, reduced intestinal motility, blind loop syndrome or stasis, or has had previous antibiotic therapy or bowel surgery, significant changes in the microflora of the bowel may be observed. When gastric secretion, intestinal motility or anatomic integrity is altered, the flora of the small bowel may be affected. Under these conditions large numbers of facultative aerobes (e.g., *Escherichia coli*) and obligate anaerobes (*Bacteroides fragilis* and other fecal anaerobes) may be found in this area. A malfunctioning ileocecal valve could permit these aerobic and anaerobic bacteria to colonize the ileum.

Problems in diagnosis: Even though the methods currently used for culturing anaerobes have been greatly improved, bacterial cultures from intra-abdominal sites can be diagnostically misleading. Anaerobes are the most often overlooked category of potentially pathogenic organisms because their detection demands meticulous collection and culture techniques. The cultivation of certain anaerobes may require up to ten days of incubation, and even a brief exposure to air can kill many of them. Multiple pathogens are frequently encountered, and one organism can overgrow another on the culture plate. Blood cultures can be similarly deceptive, since all significant pathogens in a mixed infection are rarely isolated in a single culture.

Sometimes only the consistent reappearance of a given microorganism in repeated cultures is the clue to clinical importance.

Please turn page for information on one antibiotic of significance in the treatment of serious anaerobic intra-abdominal infections.

Upjohn

Effective against susceptible anaerobes in serious intra-abdominal infections...

Anaerobic activity: Cleocin® PO₄ (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal-cuff infection caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Effective in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO₄ in gram-positive infections has been investigated both clinically and bacteriologically. Since it is a parenteral antibiotic, Cleocin PO₄ has been evaluated in serious infections. Its use in these infections should be reserved for penicillin-allergic patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Indications include: serious lower respiratory-tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease.



With few exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions.

Other therapeutic considerations:

1. Cleocin PO₄ is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO₄ is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and

intravenous corticosteroids should also be administered as indicated.

Thus, Cleocin PO₄ can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO₄ should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO₄ should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section of the brief summary on the following page.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

*Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g., *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

...and effective in serious aerobic gram-positive infections

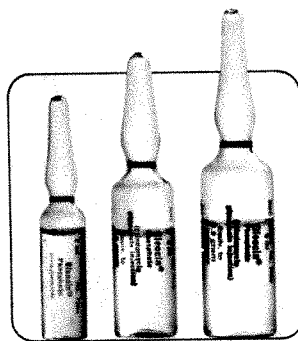
WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with the close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.



Each ml contains:
 clindamycin phosphate equivalent to 150 mg
 clindamycin base 5 mg
 benzyl alcohol 5 mg
 disodium edetate 0.5 mg
 water for injection qs
 When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible

clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2, 4 and 6 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

MED. B-4-5 (NFM-51) 7-4689-9

STERILE SOLUTION
Cleocin PO₄

clindamycin phosphate injection, Upjohn
 FOR INTRAVENOUS AND INTRAMUSCULAR USE

Upjohn

The Upjohn Company, Kalamazoo, Michigan 49001

NEW **TEVDEK II®** **and** **'silky' II POLYDEK®**

The two synthetic sutures that do not compromise your suturing technique



DEKNATEL TEVDEK II® Teflon-impregnated Dacron — This "functional monofilament" polyester suture has always been relatively stiff. Now it is remarkably soft and pliable.

If you have already tried Tевdek and found any difficulty because of stiffness, we strongly urge testing of the new Tевdek II. Please note, however, that the knotting characteristics are unchanged. Use the usual knotting technique of Tевdek.

DEKNATEL 'silky' II POLYDEK® Teflon-coated Dacron — Approximately 50% of all surgeons who tested 'silky' Polydek have been completely satisfied with its silk-like knotting characteristics. The other 50% still had problems. In our analysis, it seemed evident that a further reduction in stiffness was necessary for that other 50%.

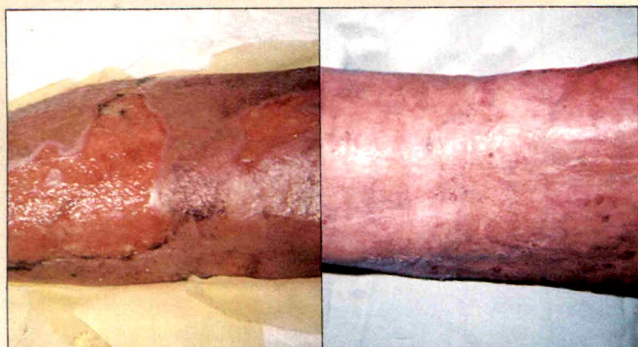
This has now been accomplished. Soft 'silky' Polydek has been improved by making it even softer (less stiff). If you have already tried the old Polydek and found any difficulty because of stiffness, we strongly urge testing of the new 'silky' II Polydek. It may be exactly what you have been searching for in the synthetics.

DEKNATEL

For further data and samples, please write—

Queens Village, Long Island, New York 11429

Because it's medicated.



Deep partial thickness burn, first 24 hours.

Complete healing after 23 days' treatment with nonadhering XEROFORM Dressings.

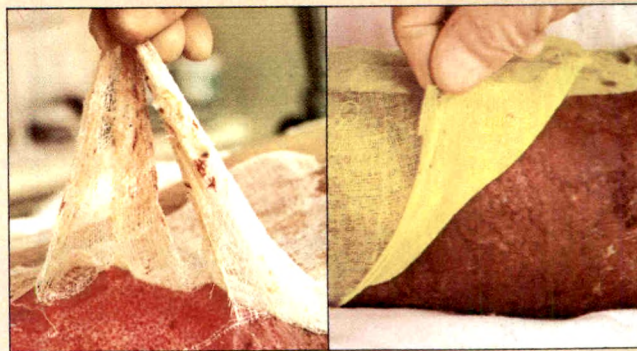
A XEROFORM Petrolatum Gauze Dressing with 3% Bismuth Tribromophenate provides an astringent action that helps maintain a dry wound...and a mild deodorizing action as well.

In addition, published data indicate that XEROFORM Dressings help promote epithelial cell proliferation:

*Human study*¹ In evaluating the effects of silver nitrate and Sulfamylon[®] on the epithelization of skin graft donor sites, Bellinger and Conway found that both agents caused delayed healing when compared to the control, XEROFORM. XEROFORM was used as the control because, in their experience, "no environment has been shown to result in faster spread of epithelium..."¹

*Animal Study*² * Using Sprague-Dawley rats, another group of investigators studied the effect of various topical dressings on donor site epithelization. They concluded: all dressings were superior to the control (exposure to air) and "Scarlet Red and Xeroform were statistically superior to all other dressings [studied] ($P < .05$)."²†

Because it's nonadhering.



Dry gauze dressings that stick to the wound can hurt and can damage new tissue.

Nonadhering XEROFORM Dressings help prevent painful reopening of wound surface—help prevent scarring and infection.

A nonadhering XEROFORM Dressing reduces pain and trauma during dressing change. It clings and conforms to all body contours—yet avoids sticking. So it lifts off easily and comfortably.

While it's on, a XEROFORM Dressing helps protect the wound from environmental contamination; helps prevent unnecessary loss of body fluids.

XEROFORM Dressings are conveniently packaged in peelable foil envelopes, with overwrap available for operating room use. Guaranteed sterile.

Sizes: 1" x 8" strips (regular and overwrap), 5" x 9" strips (regular and overwrap) and 4" x 3 yd rolls (regular only).

*Animal data are not intended to imply the same effect in humans. Human studies are now under evaluation.

†Both SCARLET RED and XEROFORM are nonadhering dressings from Chesebrough-Pond's Inc.

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**in serious or
recurrent urinary
tract infections***



Anspor[®] provides

29A

prompt clinical relief dependable bacteriological response

Clinical Efficacy

Documented results in problem infections.

Infection (due to <i>E. coli</i> , <i>Pr. mirabilis</i> or <i>Klebsiella</i> sp.)	Number of Adult Patients	Good or Excellent* Response
acute pyelonephritis	147	81%
chronic pyelonephritis	56	61%
chronic cystitis	29	62%
prostatitis	17	83%
TOTAL	249	74%

Spectrum

'Anspor' is bactericidal *in vitro* against the most frequent urinary pathogens: *E. coli*, *Pr. mirabilis*, and *Klebsiella* species.

Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Persistent urinary tract infections may require treatment for several weeks. Prolonged intensive therapy is recommended for prostatitis. In chronic urinary tract infections, frequent bacteriological and clinical appraisal is necessary during therapy and may be necessary for several months afterward.

Pharmacology

'Anspor' produces high urinary levels and is excreted essentially unchanged. (Peak concentration of approximately 3200 mcg./ml. with 500 mg. capsule in adult volunteers.)

Adverse Reactions

Adverse reactions reported in clinical trials included nausea, vomiting, urticaria, rash and joint pains. Transient rise in SGOT, SGPT, total bilirubin, and BUN has been observed. For a complete list of adverse reactions reported with

'Anspor' therapy, please see the next page.

Warning: In penicillin-sensitive patients, cephalosporins should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and cephalosporins.

*Excellent response: initial improvement at 1-3 days with maximum improvement at 2-8 days. Good response: initial improvement at 2-5 days with maximum improvement at 3-10 days. These results of clinical trials were collected from identical protocols.

For a brief summary of the prescribing information, including indications, contraindications, warnings, precautions, adverse reactions and dosage, please see the next page.

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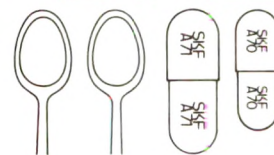
Division of SmithKline Corporation, Philadelphia, PA 19101

capsules:
250 and 500 mg.
for oral
suspension:
125 and 250 mg./5 ml.

ANSPOR[®]

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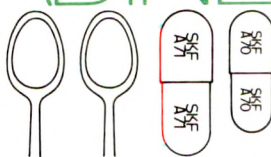
CEPHRADINE



ANSPOR[®]

brand of

CEPHRADINE



capsules:
250 and 500 mg.
for oral
suspension:
125 and 250 mg./5 ml.

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

DESCRIPTION

Anspor (cephradine, SK&F) is a semi-synthetic cephalosporin antibiotic chemically designated as 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephadrine is active against the following organisms *in vitro*:

Beta-hemolytic streptococci	<i>Escherichia coli</i>
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains	<i>Proteus mirabilis</i>
<i>Diplococcus pneumoniae</i>	<i>Klebsiella sp.</i>
	<i>Hemophilus influenzae</i>

Note—Some strains of enterococci (*Streptococcus faecalis*) are resistant to cephradine. It is not active against most strains of *Enterobacter sp.*, *Pr. morgani* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephradine and methicillin-type antibiotics.

INDICATIONS

Anspor (cephradine, SK&F) is indicated in the treatment of the following infections when caused by susceptible strains of designated microorganisms.

Infections of the respiratory tract (e.g., tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and *D. pneumoniae*.

(Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Anspor' is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of 'Anspor' in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae*, *Hemophilus influenzae* and staphylococci.

Infections of the skin and soft tissues caused by staphylococci.

Infections of the urinary tract, including prostatitis, caused by *Escherichia coli*, *Pr. mirabilis*, and *Klebsiella* species.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Cephadrine is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary.

Usage in Pregnancy and Lactation: Safety of this product for use in pregnancy has not been established. Cephadrine is secreted in breast milk during lactation.

PRECAUTIONS

Follow patients closely to detect side effects or unusual manifestations of drug idiosyncrasy. If hypersensitivity reaction occurs, discontinue drug and treat patient with usual agents, e.g., pressor amines, antihistamines, or corticosteroids.

Administer with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy as cephradine accumulates in the serum and tissues. See **DOSAGE AND ADMINISTRATION** section for information on treatment of patients with impaired renal function.

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures if superinfection occurs during therapy.

After cephradine therapy, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinistix® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®.

A positive Coombs test may be due to the drug.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: Glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn.

Skin and Hypersensitivity Reactions: Mild urticaria or skin rash, pruritus, and joint pains.

Blood: Mild, transient eosinophilia, leukopenia and neutropenia.

Liver: Transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage.

Renal: Transitory rises in BUN. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine.

Other adverse reactions have included dizziness and tightness in the chest and candidal vaginitis.

DOSAGE AND ADMINISTRATION

Anspor (cephadrine, SK&F) may be given without regard to meals. **Adults:** For skin and soft-tissue and respiratory tract infections (other than lobar pneumonia), the usual dose is 250 mg. q.i.d. in equally spaced doses. For acute infections of the urinary tract, including prostatitis, and pneumococcal lobar pneumonia, the usual dose is 500 mg. q.i.d. in equally spaced doses; severe or chronic infections may require larger doses.

Children: The usual dose is 25 to 50 mg./kg./day total, q.i.d. in equally divided and spaced doses. For otitis media due to *H. influenzae*, doses from 75 to 100 mg./kg./day in equally divided and spaced doses are recommended. Maximum dose should not exceed 4 grams per day.

All patients, regardless of age and weight: Larger doses (up to 1 gram, q.i.d.) may be given for severe or chronic infections.

In patients with impaired renal function, a modified dosage schedule is necessary. Consider each patient individually utilizing the following guideline: In adults, initial loading dose is 750 mg. and maintenance dose is 500 mg. at following time intervals: creatinine clearance >20 ml./min., 6-12 hours between doses; creatinine clearance 15-19 ml./min., 12-24 hours between doses; creatinine clearance 10-14 ml./min., 24-40 hours between doses; creatinine clearance 5-9 ml./min., 40-50 hours between doses; creatinine clearance <5 ml./min., 50-70 hours between doses. Further modification may be necessary in children.

HOW SUPPLIED

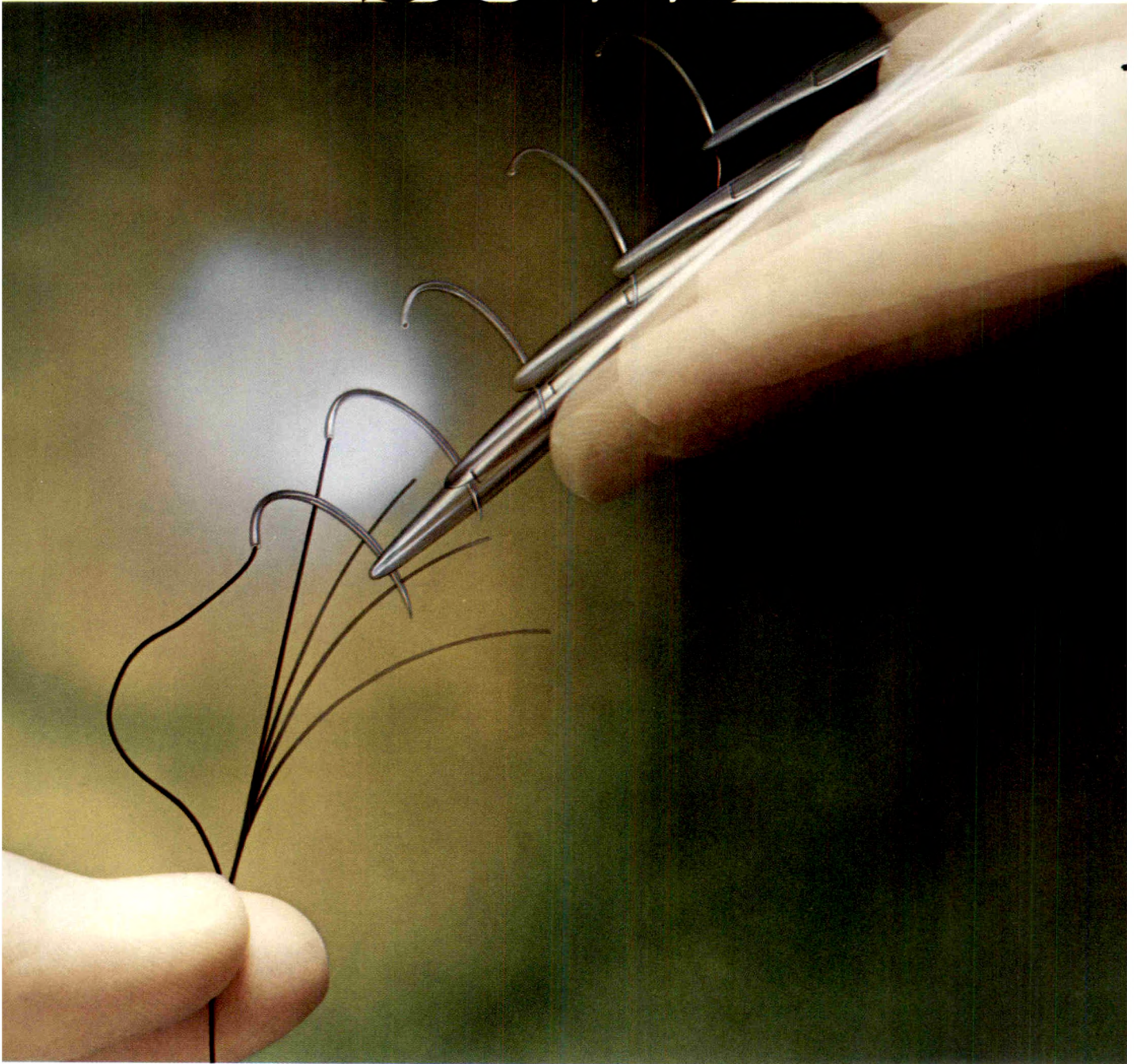
ANSPOR (cephadrine, SK&F) Capsules—250 and 500 mg.

'ANSPOR' for Oral Suspension—Pleasant fruit-flavored oral suspension which, after reconstitution, provides 125 mg. or 250 mg. of cephradine per 5 ml. teaspoonful.

an oral antibiotic from SK&F

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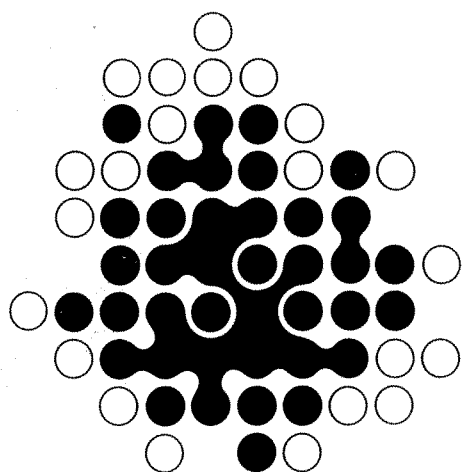


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ETHICON



CEA-ROCHE

Carcinoembryonic Antigen assay

a valuable adjunct during the
various phases of cancer management

CEA-ROCHE has been the subject of numerous clinical studies over the past four years to assess its value in cancer management. Most investigators have found this assay to be a useful biological marker for following the clinical course of patients with many types of internal carcinoma.* These studies have reported CEA-ROCHE to be a valuable adjunct in the overall evaluation of the patient's clinical progress and prognosis by indicating...

- lack of response to or escape from therapy
- need for a change or reevaluation of therapy
- development of metastases and/or local recurrence
- the need for more intensive patient examination and observation since a rise in CEA titer has been reported to precede other evidence of recurrence by periods averaging 2 months and up to as much as 29 months.*

CEA-ROCHE may also be used...

- as an adjunct to other diagnostic tests or procedures in the patient suspected of having cancer

*Literature available upon request from Professional Services Department, Roche Laboratories, 340 Kingsland Street, Nutley, N.J. 07110.

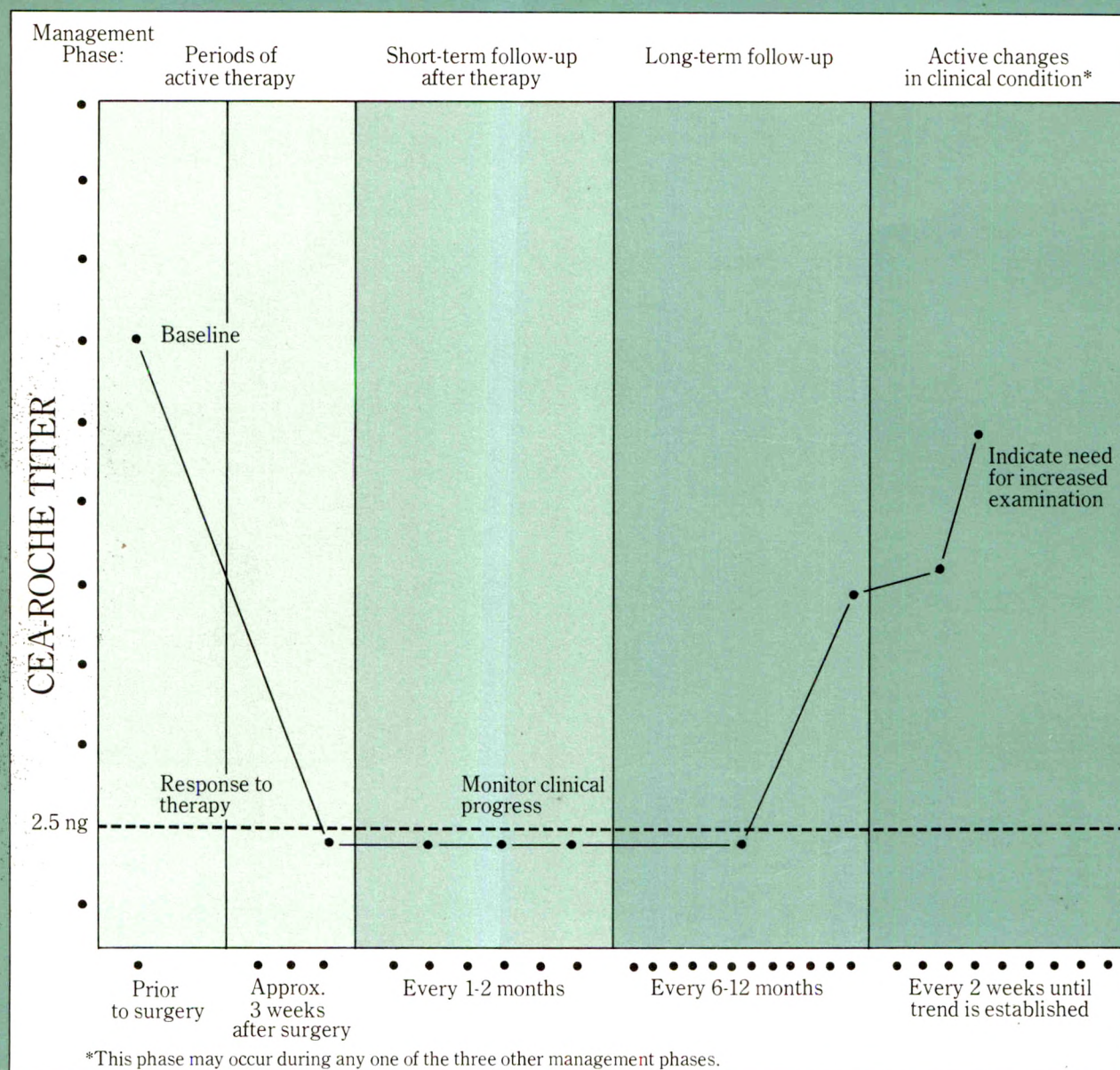
Suggested Guidelines for the Use of CEA-ROCHE^{*} as an Aid in the Management of the Cancer Patient^{*}

Type of Therapy	When to order CEA-ROCHE	Why order CEA-ROCHE
During Periods of Active Therapy		
Surgery	As part of the presurgical workup and approximately 3 weeks after surgery	To monitor the effects of surgery
Radiotherapy	Prior to initiating radiotherapy, once at midpoint and/or upon completion of radiation	To monitor the effects of radiation
Chemotherapy	Prior to initiating chemotherapy, once at midpoint if therapy extends over a 6-week period and upon completion of chemotherapy	To monitor the effects of chemotherapy
During Short-term Follow-up After Therapy		
All types	Every 1 to 2 months during the first 6 months following therapy	To provide a basis for the reevaluation of therapy and/or an early indication of recurrence or progression of disease
During Long-term Follow-up		
All types	Every 6 to 12 months	To provide an early indication of recurrence or progression of disease
During Active Change in Clinical Condition		
All types	Every two weeks until trend is established	To aid in determining the probable presence of metastases or local recurrence
When using this assay remember CEA-ROCHE is... • <i>not</i> specific for any one type of cancer • best used <i>periodically</i> to establish a trend, usually identifiable within 30 to 90 days • <i>not</i> an absolute test for malignancy and should not be used as the sole criteria for diagnosis (use with other diagnostic tests and procedures) • <i>not</i> recommended as a screen to detect cancer		
[*]These are general guidelines for the use of CEA-ROCHE only and may vary widely depending on such factors as patient status, clinical symptoms, type of malignancy, results of other tests and procedures.		



When to use CEA-ROCHE as an aid in the postsurgical management of a cancer patient

A simulation of a representative patient showing graphically when to perform CEA-ROCHE assays using the suggested guidelines appearing on the reverse side.



CEA-ROCHE may be ordered from

- Roche Clinical Laboratories, Inc., Five Johnson Drive, Raritan, New Jersey 08869 (201) 526-2400
- Major hospital and private laboratories

Additional information may be obtained from

- the Roche Representative
- the Professional Services Department, Roche Laboratories, 340 Kingsland Street, Nutley, New Jersey 07110 (201) 235-4873

Diagnostic Peritoneal Lavage in Evaluating Acute Abdominal Pain

CHARLES L. BARBEE, M.D., ROBERT B. GILSDORF, M.D., Ph.D.

A study was performed to determine the value of peritoneal lavage in the acute abdomen not related to trauma. Lavage was performed in 33 patients in the evaluation of abdominal pain of sufficient degree to warrant consideration for surgical intervention. Peritoneal lavage was truly positive or truly negative in 64% of the cases. It showed false negative results in 28% and false positive results in 8%. The lavage was most accurate in the evaluation of appendicitis, colonic disease, and intra abdominal bleeding. It was highly inaccurate in the evaluation of cholecystitis and peptic ulcer disease. It was concluded that the peritoneal lavage can be a useful adjunct in the evaluation of patients with abdominal pain and should be considered in difficult diagnostic problems but not routinely employed.

MAKING the diagnosis of the cause of acute abdominal pain and deciding whether to operate or not is often difficult. Diagnostic peritoneal lavage has been proven to be of value in the assessment of intra abdominal injuries from blunt trauma.^{7,9-12} Because of its value in these conditions, it was felt it might be of value in assessing acute abdominal problems not related to trauma. Its use for this purpose has already been suggested by Gjessing and Denker,⁴ but no objective data was published. This study was undertaken to determine what values might be applied to the laboratory analysis of peritoneal lavage fluid that could serve as a criteria for making the diagnosis of abdominal conditions requiring surgery and for deciding whether or not to operate.

Materials and Methods

Peritoneal lavage was performed as part of the evaluation of abdominal pain in 33 patients at the Minneapolis Veteran's Administration Hospital. There were 15 cases in which clinical indications for surgery were present with fairly clear preoperative diagnosis of the causes of their abdominal pain. These cases were rather classic

From the Department of Surgery, Minneapolis Veteran's Administration Hospital, Minneapolis, Minnesota and the Department of Surgery, Good Samaritan Hospital, Phoenix, Arizona

cases of appendicitis, acute cholecystitis, visceral perforation or such conditions where the diagnosis was easily made with standard clinical studies. There were 18 other cases with acute abdominal pain of the severity sufficient to warrant a surgical consult, but in which the findings were not typical enough to indicate a clear cut etiology. In the first group with clinically apparent disease, peritoneal lavage was performed in the operating room after induction of anesthesia. It was done using a small hole in the peritoneum in the central portion of the incision before the whole incision was opened. In the other cases, peritoneal lavage was performed under local anesthesia while the patient was in the ward, as described by Perry.⁸

To perform the diagnostic lavage, a peritoneal dialysis catheter (Stylocath-Abbott Laboratories) was introduced into the peritoneal cavity under direct vision. Aspiration of gross blood, bile, or intestinal contents constituted a grossly positive test. If grossly negative, a liter of lactated Ringer's solution was run into the peritoneal cavity and then allowed to drain back into the original bottle by gravity. Three separate 10 ml aliquots of the fluid were sent to the clinical laboratories for analysis. One sample was analyzed for red and white blood cells per cubic millimeter and a differential count was done on the white cells. A second aliquot was analyzed for amylase (Somogyi units per 100 ml) and for glutamyl oxylate transaminase (Carmen units per ml). The third sample was sent for bacterial culture and then centrifuged and the precipitate stained with Gram stain for bacteria. The results of the laboratory analyses of the peritoneal lavage fluid were evaluated using the criteria of Perry and Strate;¹⁰ red blood cell counts above 100,000/mm,³ white blood cell counts above 500/mm,³ amylase levels above

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Reprint requests: Robert B. Gilsdorf, M.D., Ph.D., Department of Surgery, Good Samaritan Hospital, 1033 East McDowell Road, Phoenix, Arizona 85006.

TABLE 1. *Peritoneal Lavage Values: Accurate Results*

True Positive	White Blood Cells (cells/mm ³) (%PMN/%Mono)		Red Blood Cells (Cells/mm ³)	Amylase (Somogyi Unit %)	Gram Stain	Where Performed
I Appendicitis:						
a. Acute—no perforation	2,500	90/10	591	130	neg	OR
	700	98/2	—	5	neg	OR
b. Ruptured with Free Pus	750	58/42	250	3	neg	
	2,600	90/10	440	260	G+ Cocci&Rods	OR
	100,000	—/—	100,000	—	G- Cocci&Rods	OR
c. Ruptured with Local abscess	570	—/—	0	265	neg	OR
II Cholecystitis:	1,100	95/5	2,800	58	neg	OR
III Colon Disease:						
a. Diverticulitis	970	95/5	30	1	neg	OR
	1,280	95/5	210	0	neg	OR
b. Perforation	2,800	—/—	30	87	G-Rods	OR
	5,300	93/7	5,600	2	neg	OR
IV Other:						
a. Delayed rupture of spleen	175	29/71	110,000	15	neg	Ward
b. Leaking Aortic Aneurysm	—	—/—	Gross Blood	15	neg	Ward

100 Somogyi units/100 ml and the presence of bacteria were considered to be a positive peritoneal lavage. The results of peritoneal lavage were correlated with the final diagnosis of the case as determined at surgery in 18 cases, at autopsy in one case or by clinical judgment and the hospital course of the patient in the remaining 14 cases. In addition to the clinically ill patients, three patients underwent peritoneal lavage in the operating room prior to elective abdominal surgery for non-acute conditions. The three patients served as controls.

Results

The data on all patients in which the peritoneal lavage values accurately reflected the clinical conditions are listed in Tables 1 and 2 and the data where the values did not reflect the true clinical conditions are listed in Table 3. True positive results were considered to be those in which surgery was indicated in the management of the condition and any one of the previously stated criteria were positive. True negative results were those in which

surgery was not indicated and none of the criteria were positive. Using this means of analysis, accurate results were obtained in 21 of the 33 cases, or 64%. Nine cases (28%) were falsely negative in that completely normal peritoneal lavage values were reported despite the presence of intra-abdominal infectious problems or surgical diseases. Two cases (8%) were classed as false positive because of a white count elevation in one case, and because of a report of Gram positive cocci on the stain of the precipitate in the other. In neither was surgery truly indicated.

Even though amylase and transaminase concentrations and Gram stains were obtained in all specimens, the red and white blood counts alone could have been used as criteria for positive or negative and the results of the study would have been the same. Transaminase levels were always low or normal and hence were not even tabulated. Only once was the Gram stain reported positive when the white count was not over 500 per cubic ml and that proved to be a false reading. The differential

TABLE 2. *Peritoneal Lavage Values: Accurate Results*

True Negative	White Blood Cells (cells/mm ³) (%PMN/%Mono)		Red Blood Cells (cells/mm ³)	Amylase (Somogyi Unit %)	Gram Stain	Where Performed
I Cecal Dilation due to ileus	27	44/56	1,683	20	neg	OR
II Pancreatitis	22	81/19	0	50	neg	Ward
III Granulomatous Colitis	480	76/24	350	27	neg	Ward
IV Abdominal pain, unknown etiology	100	77/23	60,000	13	—	Ward
	50	32/68	16,000	43	neg	Ward
	20	80/20	1,200	13	neg	Ward
	460	86/20	130	14	neg	Ward
	0	—/—	60	2	neg	Ward
	5	16/84	17	50	neg	Ward

TABLE 3. *Peritoneal Lavage Values: Erroneous Results*

False Negatives	White Blood Cells (cells/mm ³)	Blood Cells (%PMN/%Mono)	Red Blood Cells (cells/mm ³)	Amylase (Somogyi Unit %)	Gram Stain	Where Performed
I Appendicitis:						
a. Acute—no perforation	60	60/40	4,800	—	neg	OR
b. Ruptured with localized abscess	6	—/—	500	13	neg	OR
II Cholecystitis:	0	—/—	10	4	neg	Ward
	9	55/45	2	0	neg	OR
	29	77/21	0	17	neg	OR
III Duodenal Ulcer:	4	—/—	0	27	neg	Ward
IV Other:						
a. Incarcerated inguinal hernia	60	60/40	4,800	—	neg	Ward
b. Diverticulitis with perforation of splenic flexure of colon	5	—/—	1,200	26	neg	Ward
c. Pelvic abscess, carcinomatosis, intest. obst.	5	0/100	50	—	neg	OR
False Positive						
I Post-op glove starch granulomas	8,000	11/89	10	61	neg	Ward
II Carcinoma of pancreas	10	—/—	54	13	neg	Ward

count on the white blood cells indicated greater than 90% polymorphonuclear cells whenever the white count was elevated except for two cases. One case of spontaneous delayed rupture of the spleen and one case of peritoneal carcinoma were reported as having predominantly a monocyte elevation in the peritoneal fluid.

Three patients had elevated amylase levels. All three were in cases with free peritoneal pus or visceral perforation. The one patient eventually diagnosed as having acute pancreatitis did not have an elevated amylase in the peritoneal lavage fluid.

Eight patients had the clinical diagnosis of appendicitis made and in 6 of these, the peritoneal lavage was positive. This gives a 75% accuracy for appendicitis. One of the false negative taps for appendicitis was in a patient with a mildly inflamed appendix and it is understandable this could be missed. The second person, however, had a ruptured appendix and a localized abscess; this inflammatory reaction was in no way reflected in the peritoneal lavage.

Colonic disease was also usually reflected in the peritoneal lavage. Two cases of diverticulitis without per-

foration showed positive lavages. Here again, however, one patient with diverticulitis and a well localized perforation had a normal peritoneal lavage.

Bleeding conditions within the peritoneal cavity were accurately reflected by peritoneal lavage and proved very effective in detecting a case of delayed rupture of the spleen presenting with abdominal pain and a case of a leaking aortic aneurysm that was not clinically apparent at the time of admission to the hospital. Both had positive red blood counts on their lavage and these findings significantly influenced the course of the management of these patients in that they were rapidly taken to the operating room for treatment of their condition.

Several conditions were poorly reflected by peritoneal lavage. Peritoneal lavage proved highly inaccurate in cholecystitis; only one of four cases had a positive tap. The one case of acute duodenal ulcer had a normal tap. Incarcerated internal hernia was also not reflected by peritoneal lavage.

The three patients who had peritoneal lavage performed as part of an elective surgical procedure to determine normal values are listed in Table 4. All three of

TABLE 4. *Peritoneal Lavage Values: Normals*

	White Blood Cells (cells/mm ³)	Blood Cells (%PMN/%Mono)	Red Blood Cells (cells/mm ³)	Amylase (Somogyi Unit %)	Gram Stain	Where Performed
I As reported by Perry, et al. ⁵	<500	—/—	<100,000	<100	neg	Ward
II Normal Controls						
Patient 1	18	0/84	162	23	neg	OR
Patient 2	4	—/—	24	13	neg	OR
Patient 3	5	—/—	738	10	neg	OR

these had negative lavage values as set by a much larger patient group reported by Perry and Strate.¹⁰

Discussion

The purpose of this study was to determine the value of peritoneal lavage in the diagnosis of acute abdomen not related to trauma. The results indicate that it can be a useful adjunct in making that diagnosis but does not always reflect the true pathology present. In this study, nearly $\frac{2}{3}$ of the patients had accurate reflections of their abdominal conditions. This accuracy is nowhere near the accuracy reported in its use in the diagnosis of abdominal injuries secondary to trauma. Perry and Strate¹⁰ reported its use in 401 patients with only 0.7% false positive and 0.5% false negative results. The test was accurate in over 98% of their cases.

Laboratory studies have indicated that peritoneal lavage should be useful in the diagnosis of acute abdomen in the absence of trauma. Root and his associates¹² introduced gastric juice, bile, urine, blood and feces into the peritoneal cavity of dogs and demonstrated a peritoneal leukocytosis by peritoneal lavage. Ghanem and co-workers demonstrated a peritoneal leukocytosis following experimental superior mesenteric artery ligation in the dog, rat and mouse. Ghanem, Borner and Goodale¹ also demonstrated a potent leukotactic factor of small molecular weight in the peritoneal fluid after experimental superior mesenteric artery ligation in the rat. Waterman and Walsky¹³ found an increased level of amylase in the peritoneal fluid of guinea pigs during acute experimental pancreatitis.

Paracentesis has been advocated for making the diagnosis of the acute abdomen but has the disadvantage of having a high percentage of "dry taps"; the small amount of specimen obtained when lavage fluids are not employed makes laboratory analysis impossible⁷ and a small but definite incidence of perforation of the bowel also occurs.⁶ Keith and associates⁵ demonstrated an increased amylase level in the existing peritoneal fluid of patients with pancreatitis, high intestinal fistulas, perforated peptic ulcers and strangulated small intestine. Gjessing and Dencker⁴ reported the use of peritoneal lavage in evaluating acute abdominal pain in 7 patients. They did not report laboratory values for the fluid and apparently only examined the fluid grossly. They considered the test to be of value in their 7 cases.

All lavages in the current study were performed without complications. Perry and associates¹⁰ reported only 4 complications in over 800 peritoneal lavages employing the direct peritoneal approach; so the procedure is relatively safe.

A serious error occurs if surgery is performed because of false positive lavage. This study had two such cases. One of our false positive cases had a positive Gram stain

as the single criteria to make it positive. The other one had a leukocytosis but the differential count indicated high monocyte percentage. On the basis of these two cases, one should perhaps not use the Gram stain as sole criteria for declaring the lavage positive and a high monocyte count should make one doubt the significance of a leukocytosis especially if splenic problems are not in consideration.

In summary, this study shows that leukocytosis or greater than 500 cells/mm³ is the best indicator of a positive peritoneal lavage but a differential count should be obtained. The accuracy of the test is best in evaluating appendicitis or colonic disease but is not accurate in upper intestinal diseases. Bleeding diseases are accurately reflected. The study suggests that peritoneal lavage can be useful in evaluating patients with abdominal pain but does not suggest that peritoneal lavage be advocated as a routine procedure in all patients. When the diagnosis proves to be particularly difficult, or the patient is in a morbid or confused state precluding accurate clinical evaluation, the procedure can be performed with minimal risk and sufficient accuracy to be of value in making the decision to operate or not to operate.

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Strike-through of Moist Contamination by Woven and Nonwoven Surgical Materials

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A test is described which correlates the stress of stretching surgical gown and drape material with moist bacterial strike-through. By application of this test to a number of woven and nonwoven surgical gown and drape materials, it was found that not all of these materials, either woven or nonwoven, are impermeable to moist contamination for equal periods of time. Nonwoven disposable materials now in use range from those which remain impermeable to moist bacterial permeation through all tests while some remain impermeable for limited periods of time, and others almost immediately permeable to moist bacterial penetration. The same situation holds for woven materials. Under conditions of our test, Quarpel treated Pima tight-woven cotton cloth was impermeable to moist bacterial strike-through, through up to 75 washing and sterilizing cyclings, while ordinary linen and untreated Pima cloth permitted bacterial permeation almost immediately. These results have significance in lengthy wet surgical operations.

A NUMBER OF PROPRIETARY TESTS have been developed for the evaluation of permeability of nonwoven materials used in operating room apparel. However, quantitative information on a comparison of various nonwoven and woven materials is meager. Most tests deal with the effects of pressure without friction on either dry penetration or moist strike-through, using the amount of pressure and time as variants, with the test material being sandwiched between a weight and a bacterial spread.¹ In the tests employing pressure, a weight or a column of contaminated liquid is usually placed on a disc of the material, compressing the material against another surface.^{2,3,4} In other tests, a suction device such as an air sampler is used to draw contaminated air through the fabric.⁵

Most if not all the tests now in use are open to the criticism that they do not mimic the stresses encountered during lengthy surgical operations. Under these circumstances, stresses are often caused by unopposed

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pressure such as that exerted by an elbow against a sleeve, or by stretch or friction, often in the presence of moisture. After measuring some of the stresses of use, we devised a test with an unopposed weight supported by the test material in the presence of a standardized moist contaminant. We subjected many of the presently marketed nonwoven and woven materials to this test, and compared the results with those of a commonly-used test for transmission of moist contamination. Moreover, since we could find no data which correlated bursting or stretch tests of surgical gown and drape materials with changes in bacterial penetration or strike-through, we proceeded with the goal of collecting some quantitative information on this correlation, using weight and time as variants.

Unopposed Weight-Support Test

A suspension of *Serratia marcescens*, 10^6 per ml. in water was used as the standard contaminant. A double hammock was made of the test material by attaching a cutting of the material, approximately 16 x 40 cm. in size, on six metal posts mounted on a base. Two identical hammocks, each measuring approximately 16 x 20 cm., were formed with about a one-inch sag. One-half ml. of the bacterial suspension was released from a pipette into the seat of each hammock. In various experiments, weights of 200 grams, 500 grams, and 2 kilograms were placed in one of the hammocks while the other hammock contained only the contaminant solution without a weight. After 5, 15 and 30 minutes, a Rodac* plate was

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*The word Rodac is a mnemonic for either Replicate Organism Determination And Counting, or Rapid One-Step Disposable Agar Contact plate.



FIG. 1. Twin sling experimental setup with suspension of *Serratia Marcescens* 10.6 ml. in water in each hammock. A 2 kilogram weight is placed in one hammock while the other serves as a pressure-free control.

touched firmly to the underside of each hammock. Thus, we were able to determine the effects of various unopposed weights for various periods of time on wet strike-through contamination. Two kilograms was the estimated unopposed pressure of an elbow on the material of a gown sleeve during use, as well as approximately half the pressure applied against the front of a surgical gown when the surgeon leans intermittently against the operating table.

We compared results of the weight-support test with those of one of the most widely used contact tests, the Libman-Ullrich Rodac-sandwich test¹ in which the test material is compressed between two Rodac plates one of which contains a standardized bacterial culture. The sandwich is compressed with 100 grams of pressure. This test is ordinarily assayed at 5 seconds, 30 seconds and 1, 5, and 15 minutes. We extended this test to 30 minutes for comparison with our weight-support test.

Materials Tested

Woven materials

A. Linen cotton, double-layer*

1. New
2. Laundered and sterilized twice

B. Pima cotton†

1. Untreated, new
2. Quarpel treated‡

*Type 140 muslin of carded yarns with warp of 68 and fill of 72 per inch and Class A sheeting of carded yarns with warp of 48 and fill of 52, 2.65 yards per pound.

†100% cotton; 270 threads, 1 sq. in.; 2-ply warp; single fill; interstices 5 micra. Trade names: Barbac, Liquashield. Barbac and Liquashield are identical products of different manufacturers. Through differences in sizing, Liquashield is somewhat softer than Barbac.

‡Quarpel is a development of the U.S. Army Quartermaster. It is a fluorochemical finish in combination with a pyridinium or melamine hydrophobe which produces an exceptionally durable water-repellent finish.

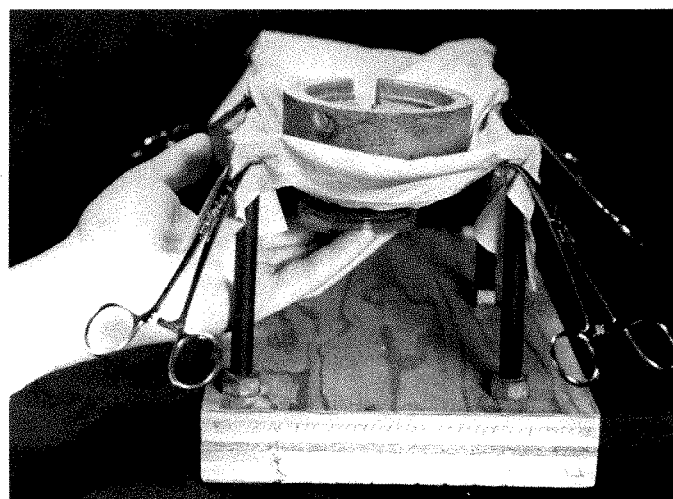


FIG. 2. Rodac plate cultures are taken from the underside of each hammock at varying periods of time.

- a. New
- b. Laundered and sterilized 2, 25, 55 and 75 cycles

Nonwoven materials

A. J & J (Barrier; Softcel)

1. Mayo stand cover; table cover
Wet-laid nonwoven fabric laminated to polyethylene film
2. Utility drape
Scrim reinforced, embossed tissue
3. Drape sheet; laparotomy sheet
Scrim reinforced, creped tissue
4. Gown
Spunlace nonwoven fabric

B. Convertors (Surg-O-Pak and Shield gown; Ameri-lon)

Scrim reinforced tissue

C. 3-M (Packs and gowns)

Spread tow plastic film composite

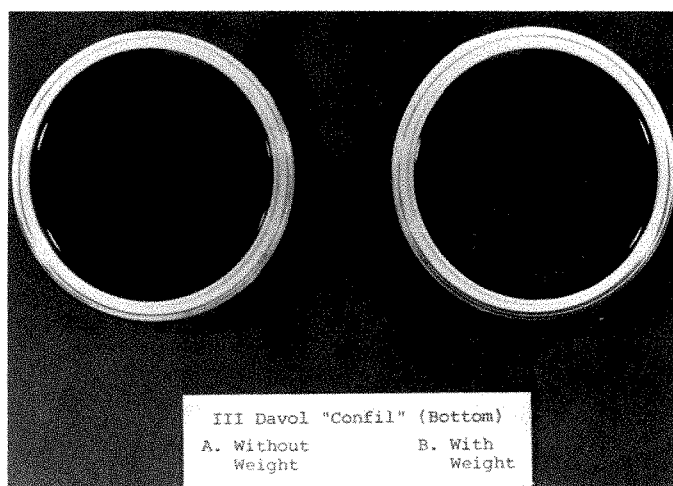


FIG. 3. Rodac plate cultures at 48 hours showing no moist bacterial strike-through when the material was not stretched by a weight. Plate on right shows positive culture in weight bearing hammock.

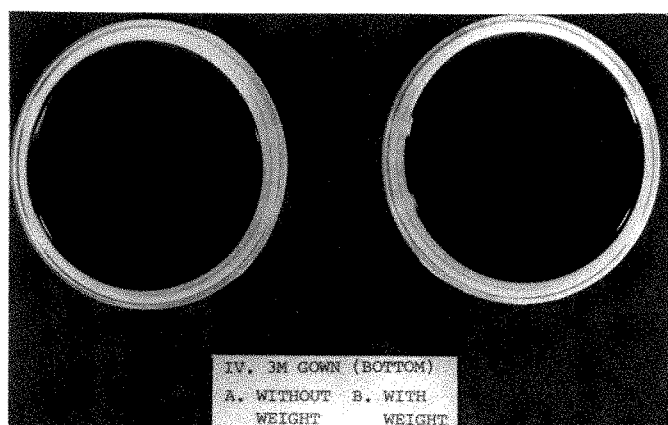


FIG 4. No bacterial strike-through in either the material not stretched by weight or that subjected to the stretch stress of the weight. This is considered a most satisfactory result demonstrating barrier effect.

- D. Macbick (Vigilon)
Spunbonded polyethylene nonwoven fabric
- E. Davol (Confil; gowns)
Wet-laid nonwoven fabric
- F. Kimberly-Clark (Kimlon Kaycel; packs and gowns)
Fiber reinforced tissue

Results

Woven materials

A great difference in wet bacterial strike-through was found between Quarpel-treated Pima tight-woven cotton cloth, on the one hand, and either ordinary linen or untreated Pima cloth, on the other. The treated Pima cloth resisted the transmission of moist contamination in all tests up to 30 minutes of stress time equally well through fifty-five washings and autoclavings. Some barrier effect was seen after as many as 75 cyclings (Table I). The ordinary linen and the untreated Pima cloth permitted

TABLE 1. *Unopposed Weight-Support Test (2 Kg. Weight)*
Bacterial Penetration = + Wovens

Material	5 min.	15 min.	30 min.
Tight weave Pima, Quarpel treated	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Tight weave Pima, Quarpel treated, 55 cyclings	0 0	0 0	0 0
Tight weave Pima, Quarpel treated, 75 cyclings	0 0	0 0	0 +
Tight weave Pima, Quarpel treated, 100 cyclings	0 0	0 +	0 +
Tight weave Pima, untreated	+	+	+
Linen, new	+	+	+
Linen, cycled twice	+	+	+

TABLE 2. *Unopposed Weight-Support Test (2 Kg. Weight)*
Bacterial Penetration = + Nonwovens

Material	5 min.	15 min.	30 min.
Spread tow plastic film composite	0 0 0 0 0 0	0 0 0 0 0 0	0 0 0 0 0 0
Wet-laid nonwoven fabric laminated to polyethylene film	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Scrim-reinforced tissue	0 0 0 0 0	0 + 0 0 0	0 + 0 0 +
Scrim-reinforced embossed tissue	0 0 0 0 0	0 0 + + 0	0 0 + + 0
Spunbonded polyethylene fabric	0 0 0 0 0	0 0 0 0 +	0 0 0 + +
Spunlace nonwoven fabric	0 0 0 0 0	0 + 0 0 0	0 + 0 + 0
Wet-laid nonwoven fabric	0 0 + 0 0 0	+ 0 + 0 0 0	+ 0 + + + +
Fiber reinforced tissue	+ + + + 0 +	+ + + + 0 +	+ + + + + +

bacterial permeation in all tests almost immediately, usually without pressure or unopposed weight stress.

Nonwoven materials

Significant differences in wet bacterial strike-through were found between the various types of nonwoven materials used in the manufacture of disposable surgical gowns and drapes. Many of these differences were demonstrable by an existing test, the Libman-Ullrich compression test, but were more obvious with the authors' unopposed weight stress test.

Of the nonwoven materials, the one which withstood

TABLE 3. *Rodac-Sandwich Test Bacterial Penetration of Nonwovens (Libman-Ullrich)*

Material	5 sec.	30 sec.	1 min.	5 min.	15 min.
Spread tow plastic film composite	0	0	0	0	0
	0	0	0	0	0
	0	0	0	0	0
	0	0	0	0	0
Scrim reinforced, crepe tissue	0	0	0	0	0
	0	0	0	0	0
Scrim reinforced, embossed tissue	0	0	0	+	0
	0	0	0	0	0
Spunlace, nonwoven fabric	+	+	+	0	0
	0	0	0	0	0
	0	0	0	0	0
	0	0	0	0	0
Wet-laid nonwoven fabric laminated to polyethylene film	0	0	0	0	+
	0	0	0	0	+
Scrim reinforced tissue	0	0	+	+	+
	0	0	0	+	+
Wet-laid nonwoven fabric	0	0	+	+	+
	0	+	+	+	+
Fiber-reinforced tissue	0	0	+	+	+
	0	+	+	+	+
	0	+	+	+	+
	0	0	+	+	+

all tests was spread tow plastic film composite. This material is used by one manufacturer in both gowns and drapes. Next in barrier effect was wet-laid woven fabric laminated to polyethylene film, a material used in the fabrication of an instrument tray cover by one manufacturer but not used in gowns or drapes, apparently because of heat-retention properties.

Four other gown and drape materials were considered

satisfactory when subjected to the unopposed-weight stress test for 30 minutes, although all of them permitted some bacterial strike-through on one of five tests at 15 minutes and two of five tests at 30 minutes. These materials were: scrim-reinforced tissue; scrim-reinforced embossed tissue; spunlace nonwoven fabric, and spunbonded polyethylene nonwoven fabric.

Two gown and drape materials, wet-laid nonwoven fabric and fiber-reinforced tissue, were found to be poor bacterial barriers. Both permitted wet bacterial penetration within five minutes in most runs of both the compression test and the unopposed weight stress test.

Tables II, III and IV show a rather close correlation between the Libman-Ullrich compression test and our unopposed weight stress test as far as the former test went. However, in separate runs, two of the materials, wet-laid nonwoven and wet-laid nonwoven-with-polyethylene could not withstand the 2 Kg weight without tearing. In other runs, these materials did not tear, but at the 30 minute reading with the 2 Kg weight test, permeation of bacteria occurred in almost twice as many specimens (7 as against 4) as had occurred at the 15 minute reading. It would appear that 15 minutes is an insufficient length of time to test for bacterial penetration if the test is to be applied realistically to the lasting barrier effect through lengthy surgical operations.

Not shown in the tables was the testing carried out for permeability of the stockinette cuffs found on virtually every surgical gown whether the gown was made of woven or nonwoven material. In every test the stockinette acted as a wick, permitting almost immediate strike-through of wet bacterial contamination without applying a stress factor.

Discussion

Bacterial impenetrability, freedom from hazard, and economy are considered to be the ideal characteristics of

TABLE 4. *Unopposed Weight-Support Test Average Bacterial Penetration at Indicated Periods Under Variable Weights*

Material	200g.			500g.			2Kg.		
	5 Min.	15 Min.	30 Min.	5 Min.	15 Min.	30 Min.	5 Min.	15 Min.	30 Min.
Pima treated with Quarpel	0	0	0	0	0	0	0	0	0
Spread tow plastic film composite	0	0	0	0	0	0	0	0	0
Wet-laid nonwoven with polyethylene	0	0	0	0	0	0	Could not withstand weight		
Scrim reinforced tissue	0	0	0	0.17	0.17	0.67	0.67	0.83	1.0
Scrim reinforced crepe	0	0	0.50	0.17	0.17	0.67	0.67	0.83	1.0
Scrim reinforced embossed	—	—	—	0.33	0.64	0.83	—	—	—
Spunlace, nonwoven	0	0.50	0.67	0.83	0.83	0.83	0.83	1.0	1.0
Wet-laid, nonwoven	0.17	0.50	0.83	0.33	0.83	0.83	Could not withstand weight		
Linen	—	—	—	0	0.33	0.83	1.0	1.0	1.0
Pima, untreated	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Spunbonded	0	0.33	1.0	—	—	—	—	—	—
Fiber reinforced	0.87	0.87	1.0	—	—	—	—	—	—

— = Not assayed

TABLE 5. *Rodac-Sandwich Test (Libman-Ullrich) Average Bacterial Penetration After Specified Exposure Times*

Material	5 Sec.	30 Sec.	1 Min.	5 Min.	15 Min.
Pima cotton treated with Quarpel	0	0	0	0	0
Spread tow plastic film composite	0	0	0	0	0
Scrim-reinforced embossed tissue	0	0	0	1.0	0
Scrim-reinforced crepe tissue	0.25	1.25	0.50	0	0
Spunbonded polyethylene nonwoven	0.20	0.20	0.20	0.20	0.20
Wet-laid nonwoven laminated to polyethylene film	0	0.33	0.50	1.0	3.17
Spunlace nonwoven	0.80	1.20	1.60	1.60	2.60
Pima, untreated	0.20	0.60	1.20	1.60	4.0
Scrim-reinforced tissue	0	0	1.0	3.50	4.0
Wet-laid nonwoven	0	2.0	2.5	4.0	4.0
Fiber reinforced tissue	0.75	1.5	2.75	4.0	4.0
Linen	3.4	4.0	4.0	4.0	4.0

operating room apparel and drapes. Other sought-after goals are comfort, convenience, and dependable sterility. Manufacturers usually guarantee sterility upon shipping from the factory. The shelf-life of the sterile contents of a package is essentially a product of the packaging. From the user's point of view, first and foremost among the characteristics of barrier materials is the capability of the material to prohibit the transfer of bacteria under the conditions of use in the operating room. A number of tests have been devised by the single-use hospital product industry to assay the bacterial barrier properties of the various materials used for surgical apparel, drapes, and packaging materials for sterile products (Table VI).

Many of the nonwoven gown and drape materials are being promoted as barriers to wet contamination. However, in a random survey, Rodac plate cultures of some disposable gowns and drapes taken during actual surgical operations which lasted more than one hour, we found many positive cultures, especially in places on the gowns

or drapes where moisture and physical stresses had occurred, such as the axillary region and front of nonwoven gowns and the unreinforced areas of woven gowns. Identification of organisms in these cultures yielded mainly Staph. epidermidis and occasional Staph aureus, indicating that the source of contamination was mainly the wearer. When members of the surgical team wore woven gowns in which the front and sleeves were reinforced with treated, tight-woven Pima cloth, positive cultures of Staph. epidermidis could only be obtained from areas of the gown which were not reinforced. Cultures of the enforced areas were either sterile or yielded growths of gram-negative types such as E. coli species, which were more likely to come from the surgical site, especially during operations on the intestinal tract, than from the surgeon's body. These findings aroused sufficient curiosity about barrier standards, we felt, to warrant a closer look at the tests being used to determine the barrier effect of these materials.

Our test provides continuous stress for up to 30 minutes. The conditions of the test can be criticized as being too stringent, since stresses during surgical operations tend to be intermittent. However, results at 30 minutes correlated well with cultures taken after one hour of actual use during surgical operations.

Inasmuch as the gown materials cannot be looked upon as bacterial filters, the transmission of moisture is tantamount to the transmission of contained bacteria. Beck and Mandeville⁷ have described a continuous waterpressure test for testing barrier materials for moisture transmission but did not correlate results with bacterial strike-through. Transmission of dry particles containing bacteria through loosely woven gown material was demonstrated by Charnley and Eftekhari.⁸

The finding that some woven and some nonwoven materials can withstand actual and simulated operating room stresses without losing their barrier effect, while others retain a barrier effect only for limited periods of time or not at all, would appear to carry several practical implications for both manufacturers and users.

TABLE 6. *Industrial Testing Protocol*

Basis Weight	Taber Abrasion (Wire)	Fire Retardancy (Machine Direction)
Mullen (Bursting Strength)	Wet Taber Abrasion (Felt)	Fire Retardancy (Cross Direction)
Thickness	Wet Taber Abrasion (Wire)	Bacterial Penetrability
Air Permeability	Tear (Machine Direction)	Free Lint
Tensile (Machine Direction)	Tear (Cross Direction)	Surface Resistivity (front)
Tensile (Cross Direction)	Spray Rating	Surface Resistivity (back)
Stretch (Machine Direction)	Hydrostatic Head	Voltage Decay (front)
Stretch (Cross Direction)	Water Repellency	Voltage Decay (back)
Grab Tensile (Machine Direction)	Absorbency	Binder Analysis
Grab Tensile (Cross Direction)	Absorptive Capacity	Fiber Analysis
Grab Stretch (Machine Direction)	Fire Retardancy (Machine Direction)	Tensile Energy Absorption
Grab Stretch (Cross Direction)	Fire Retardancy (Cross Direction)	Bacterial Strike-Through
Cantilever Stiffness		
Taber Abrasion (Felt)		

Gowns made of ordinary linen or of nonwoven materials which are not barriers appear to be suitable for short or relatively dry operative procedures, but according to our data, are not suitable for more lengthy or wetter operations. Such in-use differences in bacterial permeability of various gown and drape materials have not heretofore been brought to the attention of the users.

Areas of greatest risk of moist strike-through contamination appear to be the sleeves and front of the surgical gowns and the roughly two-foot-wide area surrounding the fenestra of surgical drapes. Some commercially available gowns and drapes, both woven and nonwoven are reinforced in these areas with a relatively impermeable layer. Yet curiously, most surgical gowns, both woven and nonwoven, have stockinette cuffs whose wicking effect would tend to negate whatever barrier effectiveness the gown material may possess. Ideally, these cuffs remain covered by the surgeons glove during an operation and therefore should remain dry. But in practice the cuffs often become uncovered and wet, especially during lengthy major operations. Inquiry was made of manufacturers as to why they knowingly outfit their gowns with stockinette cuffs. The response was that this was the preference of surgeons because they hold snugly to the wrists. We would recommend a creping or pleating of impermeable material for a fitted cuff rather than stockinette. We would also recommend investigation of the possibility of treating nonwoven materials with a waterproofing process similar to that used for woven materials.⁸

Although lamination of nonwoven materials with a plastic layer provides a complete barrier effect, the lamination can only be used for instrument-table covers and similar uses not involving covering the body of the patient or the bodies of the members of the surgical team because of the great heat-retaining property of the plastic layer. Tightly woven materials have essentially the same heat-retaining qualities as plastic lamination. When plastic lamination or tightly-woven materials are used to make an entire gown or drape, it is essential to provide some form of ventilation for the body under the material. This is basically the rationale behind the vacuum apparatus used with the coverall surgical gown made completely of tightly woven waterproofed Pima cloth.

Conclusions

Not all woven and nonwoven surgical gown and drape materials are impermeable to moist contamination for equal periods of time. Under the conditions of our tests,

Quarrel-treated Pima tight-woven cotton cloth was impermeable to moist bacterial strike-through equally well after up to 75 washing and sterilizing cyclings. Ordinary linen and untreated Pima cloth, on the other hand, permitted bacterial penetration almost immediately.

Among the nonwoven gown and drape materials, spread tow plastic film composite remained impermeable to moist bacterial penetration throughout all tests. Another material, wet-laid woven fabric laminated to polyethylene film also withstood the tests, but is used only in the fabrication of an instrument tray cover and not in gowns and drapes because of its heat-retaining properties. Four other nonwoven gown and drape materials were considered satisfactory, but not as consistently impermeable as the spread tow plastic film composite. These were scrim-reinforced tissue, scrim-reinforced embossed tissue, spunbonded polyethylene nonwoven fabric, and spunlace nonwoven fabric. Two gown and drape materials were found to be poor bacterial barriers, allowing wet bacterial penetration within five minutes in most test runs. These were wet-laid nonwoven fabric and fiber-reinforced tissue.

The stockinette material of gown cuffs permits immediate passage of wet contamination.

In our opinion, tests for bacterial permeability should be restudied from the standpoint of correlating bacterial permeation with the type of stresses encountered during actual surgical operations of varying length and complexity.

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Survival Improvement Following Aortic Aneurysm Resection

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Abdominal aortic aneurysm resections were performed on 298 patients between January, 1966 and December, 1973. The results were compared with 186 resections previously reported between 1955-1965. Hospital mortality rates for elective resections were 13% in 1955-1965, 8.4% in 1966-1973, and 4.2% in the 113 patients treated during the last 3 years. Urgent resections for intact aneurysms, previously associated with a 36% mortality, resulted in a 6% mortality rate in 1966-1973. The emergency resection mortality rate for ruptured aneurysm, originally 69%, was reduced to a present day over-all mortality of 55%, and 42% for the last 3 years. Calculated actuarial survival at 5 years was 65% for urgent (intact), 60% for elective and 40% for emergency (ruptured) groups. Atherosclerosis remains the major deterrent to long-term survival with myocardial infarction and stroke causing 43% of deaths occurring within 5 years. Improved survival appeared secondary to better operative technique, postoperative patient monitoring, increased surgical experience, and more elective resections of smaller, asymptomatic aneurysms than in 1955-1965. With present day low mortality rates, elective resection should be recommended in all patients without significant medical contraindications.

ABDOMINAL aortic aneurysmectomy became a common operation after 1952, when Dubost et al. first described a successful aortic resection and graft replacement.¹² In 1968, 186 consecutive aneurysm resections analyzed with regard to preoperative management, operative technique and surgical results were reported from this institution.²⁶ This report is based on a study of 298 patients who have had resections of abdominal aortic aneurysms performed by the full-time attendings and residents at the University of Rochester Medical Center between June 1966 and December 1973.

Material and Methods

Because of the marked difference between the operative mortality of intact and ruptured aneurysms, our present data, as in a previous publication, is divided into three groups: Group I, ruptured aneurysms (bleeding present in

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the retroperitoneum or peritoneum); Group II, intact aneurysms having urgent resection because of acute expansion, increasing pain or possibility of rupture; Group III, electively resected aneurysms.²⁶

Patients who had resection of their aneurysm with graft replacement or died during performance of the operation were included. Fifteen patients who had wiring of their aneurysm and 5 who had ligation of the aorta with insertion of axillofemoral grafts were excluded. The inclusion of these alternative methods of treatment would not significantly alter the over-all mortality rates and will be reported elsewhere.

Emergency Resection of Ruptured Aneurysm (Group I)

There were 56 patients (47 men, 9 women) in this group, ranging in age from 60-80 years (average 69-years-old). Eighty per cent of the patients had arteriosclerotic heart disease (ASHD) on the basis of documented past myocardial infarctions or a history of angina (Table I).

If the diagnosis of ruptured abdominal aortic aneurysm was suspected clinically immediate preparations were made for transporting the patient to the operating room and all such patients were included in the study. Forty-four patients (82%) were in shock (systemic blood pressures SBP less than 90 mm Hg/60 mm Hg) prior to surgery. Preoperative preparations included introduction of large bore intravenous lines in one or both arms for volume replacement, insertion of a subclavian central venous pressure (CPV) line for monitoring, passage of an indwelling urinary catheter, insertion of a nasogastric tube, administration of antibiotics and the typing and cross matching of at least 6 units of whole blood.

After aseptic preparations of the abdomen, a long midline incision was used to enter the peritoneal cavity.

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TABLE 1. *Summary of Group Data*

	Male:Female	ASHD	Age (Average)
Elective	185:40	70%	67 y/o
Urgent	13:4	59%	70 y/o
Ruptured	47:9	80%	69 y/o

There were large retroperitoneal hematomas in all patients and free intraperitoneal blood in 40%. Control of the aorta was obtained in all cases either through the gastrohepatic or gastrocolic ligaments. Another clamp was then placed in the infrarenal position as soon as feasible in order to minimize renal ischemic time. After distal control of the iliac vessels, the aneurysm was opened and bleeding lumbar arteries were oversewn. No aneurysms were completely resected and woven Dacron bifurcation grafts were used for reconstruction with distal anastomoses made to the common iliac or external iliac arteries in 70% of the patients and to the common femoral arteries in 30% of them. Declamping hypotension was minimized by adequate blood replacement and testing of the proximal anastomosis prior to beginning the distal anastomoses. Mannitol and volume replacement were used if prolonged supra-renal cross-clamping was necessary or diminished urinary output was evident.

No intra-operative deaths during resection were excluded from this series.

Postoperatively all patients were admitted to the surgical intensive care unit where monitoring of systemic blood pressure, CVP, urinary output, abdominal girth, peripheral pulses and hematocrit were carried out.

Urgent Resections of Intact Aneurysms (Group II)

There were 17 patients presenting with increasingly severe symptoms of suspected aortic aneurysm expansion or rupture. There were 13 men and 4 women with an average age of 70 years. Fifty-nine per cent had ASHD (Table 1). No preoperative hypotension, anuria, or acute electrocardiographic (ECG) changes were present in these patients. Operation was scheduled as an urgent procedure after preoperative preparations were completed. Infrarenal aortic control was most often attained initially, systemic heparinization was always used, and pre-clotted knitted, rather than woven, Dacron prostheses were frequently employed. There was no evidence of retroperitoneal blood but intramural fresh hematomas were present in 24% of the patients. No aneurysms were completely resected and distal anastomoses were made

TABLE 2. *Hospital Mortality for Aneurysm Resection (1966-73)*

Classification	# Pts	Deaths	% Hosp. Mortality
Ruptured	56	31	55
Urgent	17	1	6
Elective	225	19	8.4

to the distal aorta in 12%, common iliac and external iliac arteries in 78% and common femoral arteries in 10% of the patients. The grafts were wrapped with the residual sac and the peritoneum was closed carefully to avoid the duodenum and superior mesenteric vein.

Elective Aneurysm Resection (Group III)

There were 225 patients (185 men and 40 women) with an average age of 67 years, who underwent elective aneurysm resection. Seventy per cent had ASHD (Table 1). Routine preoperative evaluation and preparation for surgery were carried out as previously described. In 37% of cases, the aneurysm was totally resected, while in the remainder the pre-clotted knitted Dacron or woven grafts were covered with the residual sac and peritoneum. Distal anastomoses were made as follows: distal aorta (10%), common iliac and external iliac arteries (74%), common femoral arteries (16%). Additional procedures after aneurysm resection and reperitonealization included: one cholecystectomy, one colectomy, one inguinal herniorrhaphy, three tracheostomies, two gastrostomies, one renal artery reconstruction, and one bilateral nephrectomy.

Results

Group I

Fifty-five per cent of these 56 patients died in the hospital or within 30 days of operation during the period 1966-1973 (Table 2). The mortality rate was 42% during the period of 1971-1973. Free intra-abdominal bleeding, present in 40% of the patients, was associated with a 57% mortality rate, while patients with contained ruptures had a 48% mortality rate. Arteriosclerotic heart disease (ASHD) was not a significant determinant of operative survival. There was a 26% mortality rate in patients with pre-existing ASHD contrasted to a 66% rate in patients without ASHD. Preoperative shock was associated with a 67% mortality rate as compared to a 25% mortality rate in patients without shock. Advancing age resulted in a linear increase in mortality rate from 33% in the 50-59 year age group to 100% in those over 80 years old (Table 3).

Postoperative complications occurred in 84% of the patients (Table 4). Renal failure (70% mortality rate), myocardial infarction (100% mortality rate) and bleeding were the major causes of postoperative death. Pulmonary insufficiency occurred in 2 patients without mortality.

The actuarial survival rates indicate that 31 patients died intra-operatively or within 30 days, and 2 additional patients died within 1 year (Table 5) (Fig. 1). Thereafter, no deaths occurred in the at-risk group for 5 years.

Group II

The hospital mortality for 17 patients was 6% for 1966-1973 (Table 2). ASHD was present in 60% of the patients and was associated with a 9% mortality rate, as

TABLE 3. *Operative Mortality—Age Related*

Group	# Pts Age 50-59	Mortality Rate (%)	# Pts Age 60-69	Mortality Rate (%)	# Pts Age 70-79	Mortality Rate (%)	# Pts Age 80-	Mortality Rate (%)
Elective & Urgent	42	0	95	6	95	13	14	7
Ruptured	9	33	20	35	23	74	4	100

compared to 0% in those without ASHD. An actuarial survival curve paralleled the elective group curve with a 65% 5-year survival (Fig. 1). Late deaths were caused by myocardial infarction (2 patients), aspiration pneumonia (1 patient), and pulmonary embolus (1 patient) (Table 5).

Group III

The hospital mortality rate was 8.4% in 1966-1973 and 4.2% for 1971-1973 (Table 2 and Fig. 2). Pre-existing ASHD was associated with a 9% operative mortality rate while no hospital deaths occurred in patients without ASHD. The mortality rate in the 80 plus age group was similar to the 60-69 year olds (Table 3). There was a 13% mortality rate for the 70-79 year old age group, but this group was heavily weighted by patients operated upon early in the series with 70% incidence of ASHD.

Postoperative complications were present in 40% of the patients (Table 4). Myocardial infarction (10 deaths), and renal failure requiring dialysis (4 deaths) comprised the most frequent fatal complications. Operative site bleeding required re-exploration of 15 patients with three mortalities. Pulmonary insufficiency complicated by pneumonia resulted in a 33% mortality in 6 patients and peripheral embolism requiring removal by Fogarty catheters occurred in 6 patients with the loss of one limb and no associated deaths. No patient survived a post-operative cerebrovascular accident (CVA) (3 deaths), and 6 graft infections resulted in 1 death.

Actuarial analysis revealed a 60% five-year survival

(Fig. 1). Myocardial infarction and strokes caused 41% and 2% of late deaths respectively and carcinoma, 23% (Table 5). The cause of 25% of the late deaths was not known.

Discussion

What is the expected mortality rate for resection of abdominal aortic aneurysms? In order to answer this question, reported series of aneurysm resections from 1955 to the present were reviewed and representative series of different sizes were combined to obtain a good group of mortality rates for aneurysm operations. This method can be criticized on the basis of differing patient populations, surgical techniques, experience of operators, size of aneurysms and degree of atherosclerosis, yet it represents one method of establishing the mortality rates of procedures done by independent surgeons during a concurrent period (Tables 6-9).

The group hospital mortality rates for ruptured abdominal aortic aneurysms prior to 1966 was 53% for 765 patients (Table 6). Two series overlapped, but the number of patients involved, 72, was not significant. In comparison, since 1966, 11 series with 372 patients had an average group mortality rate of 45%. There was an overlap from pre-1966 present in 5 series, thus representing a high estimation of average mortality rate (Table 7). Improvement in the results of ruptured aneurysm treat-

TABLE 4. *Postoperative complication*

Complications	Ruptured		Elective & Urgent	
	# Pts	# Deaths	# Pts	# Deaths
None	9	0	151	0
Renal failure	10	7	9	4
Myocardial infarction	13	13	16	10
Bleeding-operative site	9	6	15	3
gastrointestinal	5	2	2	0
Stroke	1	1	3	3
Pulmonary insufficiency	2	0	6	2
Pulmonary emboli	2	1	3	0
Graft infection	3	2	6	1
Venous thrombosis	6	0	0	0
Peripheral embolism	2	0	6	0
Small bowel obstruction	1	0	4	0
Arrhythmias	4	1	23	2

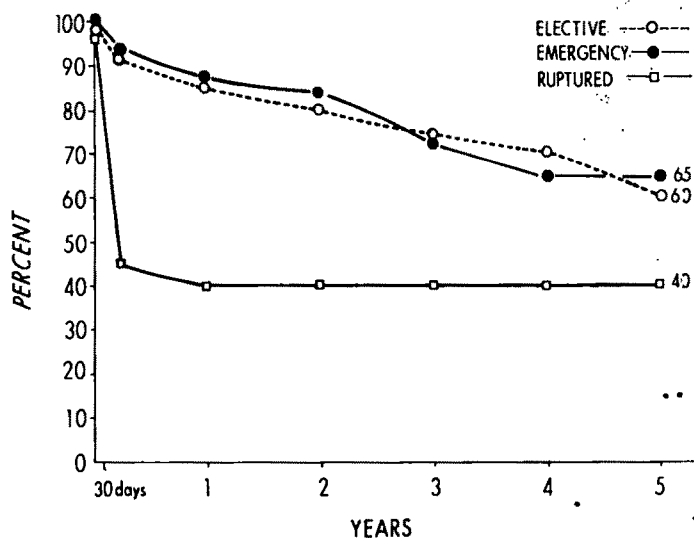


FIG. 1. Actuarial survival following aneurysm resection.

TABLE 5. Causes of Late Deaths in Hospital Survivors

Cause of Death	Ruptured Aneurysms		Intact Aneurysms			
	# Pts	Late Death (%)	Urgent		Elective	
			# Pts	Late Death (%)	# Pts	Late Death (%)
Myocardial infarction			2	50%	18	41%
Cancer (lung, pancreas, ovary, bladder)	1	50%			10	23%
Stroke					1	2%
Infected graft with anast. breakdown					2	5%
Infected graft with sepsis					1	2%
Pulmonary embolus			1	25%		
Unknown	1	50%			11	25%
Pancreatitis					1	2%
Pneumonia (aspiration)				25%		

ment appears to be limited by the basic lethality of the lesion. Shock, preoperative oliguria, and delay of diagnosis have all been cited as major deterrents to operative survival. Our personal series reveals a mortality rate of 55% since 1965 and 42% from 1971-1973. In comparison with the previous report from this institution, an analysis reveals that fewer patients from the current series died from preoperative shock (67% vs 77%) and fewer developed postoperative renal dysfunction (18% vs 30%).²⁶ ASHD made no difference in operative survival in the current series as in the previous series.²⁶

Four series included an urgent intact operative group for comparison.^{5, 26, 31, 33} (Table 8). Other reports included urgent intact and ruptured aneurysms together with expectedly lower mortality figures and these were

not included in our tabulations. In the accumulated group of 135 patients, the group mortality prior to 1966 was 26%, well below that of the ruptured group, but significantly higher than the elective mortality rate for that period. Since 1966, the mortality rate has dropped to 5.4%, closely paralleling elective operations (5.2%) (Table 9). These figures represent the strongest argument for aggressiveness in the treatment of abdominal aortic aneurysm, especially when symptoms are present.

The group mortality rate for elective resections of aneurysms was 10.5% in the pre-1966 series, and 5.2% post-1966, emphasizing a downward trend in mortality rate with experience (Tables 8 and 9). The latter figure is a high estimate because of pre-1966 overlap in 5 series. Our mortality rate has improved steadily from 21.9% in 1955-1960 to 4.2% in 1971-1973 (Fig. 2). This is due to a combination of factors which deserve mention. Patient selection has changed somewhat; patients with smaller or asymptomatic aneurysms currently are electively resected more often. Operations for smaller aneurysms proba-

TABLE 6. Cumulative Reported Series—Ruptured Aneurysms (Through 1966)

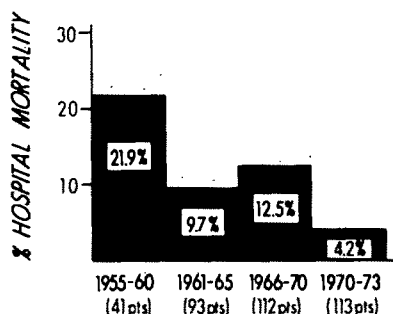
Year of Report	authors	Period	No. Patients	Hosp. Mortality (%)
1959	Sheranian et al. ²⁹	53-57	6	50
1961	Grysky et al. ¹⁸	57-60	25	58
1961	MacVaugh and Roberts ²⁴	53-60	26	85
1963	Vasko et al. ⁶	-63	34	74
1963	Voorhees and McAllister ³⁵	-63	34	76
1964	DeBaakey et al. ⁷	-64	276	34
1964	Mannick et al. ²⁵	-64	25	32
1966	Szilagyi et al. ³¹	52-65	78	60
1967	Kouchoukos et al. ³¹	58-66	36	61
1968	May et al. ²⁶	58-65	41	69
1969	Dodenhoff and Cox ¹¹	57-66	37	86
1970	Van Heeckeren ³³	56-63	31	58
1970	Alpert and Parsonnet ⁴¹	61-68	40	69
1970	Gardner et al. ¹⁷	64-65	8	88
1972	Williams et al. ³⁶	62-68	32	65
1973	Stokes and Butcher ³⁰	58-66	36	61
Total			765	53%

*Patient included past 1966, no yearly breakdown present.

TABLE 7. Cumulative Reported Series—Ruptured Aortic Aneurysms (Recent)

Year of Report	Authors	Period	No. Patients	Hosp. Mortality (%)
1970	Van Heeckeren ³³	64-69	26	62
1970	Gardner et al. ¹⁷	66-68	16	37
1970	Darling ⁸	61-68	60	40
1972	Williams et al. ³⁶	68-71	46	34
1972	Yashar et al. ³⁸	58-70	32	56
1972	Lagaaij et al. ²²	58-70	100	38
1972	Szilagyi et al. ³²	66-70	?	43
1973	Stokes and Butcher ³⁰	65-71	13	15
1973	Key and Sokol ²⁰	66-72	49	43
1973	Rainer et al. ²⁷	-73	12	17
Present series		66-73	56	55
Total			372	45
			Group Mort.	

FIG. 2. Mortality rate for elective aneurysm resection.



bly carry a lower mortality rate.³¹ The average age for the pre- and post-1966 series was similar (67 years). The current series had more patients with ASHD (70% vs 55%) and more in-hospital mortalities due to cardiac failure. (52% vs 17%).

The hospital survival of patients following abdominal aortic aneurysm resections has steadily improved since the early 1950's. Darling, in 1970, noting a 4% mortality rate, indicated that with few exceptions, all patients with a palpable aneurysm should have a resection.⁶ Szilagyi listed the following contraindications: 1) history of an MI within 3 months; 2) intractable congestive heart failure; 3) intractable angina; 4) severe pulmonary disease; 5) incapacitating residuals from CVAs; 6) renal function impairment with a creatinine greater than 3.0 mgm/100 ml; 7) associated lethal disease with less than 3 year survival expectation; 8) asymptomatic less than 6 cm size aneurysms in a patient over 75 years of age.³¹ Our previous series encouraged an aggressive approach noting that renal disease, severe ASHD, or pulmonary disease

should be relative contraindications to elective resection. However, with any change in the baseline status, such as increasing pain, or size, gratifying results were obtained with urgent resections.

Preoperative care presently includes overnight hydration with lactated Ringer's solution prior to surgery and prophylactic antibiotic coverage, a practice previously not considered routine. The role of intra-operative experience and technique may be the most significant factor in improved results. The belief that experience does improve operative results is born out by a reduction in operative mortality in all consecutive series reviewed.^{6,7,20,26,32} Furthermore, 63% of posterior aneurysm walls were left intact compared with 21% in the past series with injury to the inferior vena cava or iliac veins a rare problem (1.5% of cases).

Postoperative care and increased knowledge of postoperative complications have improved the survival results. The operative mortality reduction since 1970 is coincidental with a restructuring of the intensive care unit and improved house staff coverage. (Fig. 2) Pulmonary insufficiency was recognized early with only 2 related deaths. This 0.66% mortality rate is significantly less than the 3.4% to 19% reported in other series.^{5,11} Postoperative arrhythmias were frequent (10%) but death related to this problem was less than 1%. Renal failure requiring dialysis was reduced from 14% to 3.7% but the death rate of 22% was not significantly altered from the figure of 28% in our previous series.²⁶

The patient population was also analyzed for long-term survival and actuarial curves calculated¹³ (Fig. 1). The

TABLE 8. Cumulative Reported Series Elective and Urgent Aneurysm Resections (Through 1966)

Year of Report	Authors	Period	Number of Patients		Hospital Mortality (%)	
			Elective	Urgent	Elective	Urgent
1959	Sheranian et al. ²⁹	53-57	104		14	
1961	MacVaugh and Robert ²⁴	53-60	81		11	
1961	Gryski et al. ¹⁸	53-60	124		10	
1963	Vasko et al. ³⁴	52-62	136		10	
1963	Voorhees and McAllister ³⁵	54-62	169		18	
1963	Cannon et al. ⁴	54-62	66		15	
1964	DeBaakey et al. ⁷	52-62	1186		7	
		62-64	533		5	
1964	Hardin ¹⁰	54-63	109		8	
1966	Szilagyi et al. ³¹	52-65	309	92	13	21
1966	Levy et al. ²³	57-64	100		17	
1967	Bernstein et al. ³	55-60	85		11	
1967	Friedman and Hufnagel ¹⁶	65-66	100		4	
1968	May et al. ²⁶	55-65	146	11	15	33
1969	Foster et al. ¹⁵	54-65	116		18	
1970	Couch et al. ⁵	59-66		9		18
1970	van Heeckeren ³³	56-63		23		39
Total			3604	135	10.5%	26%
			Grp. Mort.			

TABLE 9. Cumulative Reported Series—Elective and Urgent Aortic Aneurysm Resection (Recent)

Year of Report	Authors	Period	Number of patients		Hospital Mortality (%)	
			Elective	Urgent	Elective	Urgent
1970	Alpert and Parsonnet ¹	61-68	100		2	
1970	Darling ²	61-70	155		2.6	
1970	Baker and Roberts ²	6-69	145		2.7	
1970	van Heeckeren ²³	64-69	34	22	12	5
1970	Gardner et al. ¹⁷	66-68	39		8	
1972	Williams et al. ³⁶	68-71	66		7.4	
1972	Yashar et al. ³⁸	58-70	105		5.6	
1972	Szilagyi et al. ³²	58-70	70		7	0.2
1972	Lagaaij et al. ²²	58-70	300		6	
1973	Key and Sokol ²⁰	66-72	82		0	
1973	Stokes and Butcher ²⁰	65-71	87		4	
Present series		66-73	225	17	8.4	6
Total			1408	39	5.2	5.4
				Grp. Mort.		

actuarial method used to compute survival is considered reliable. It includes all patients who survived, died, were lost to followup, removed, or at risk during a given interval. It encompasses operative and hospital mortality and accurately reflects time-related survival in a large group of patients.¹³ Using this method, 5-year survival in the elective—urgent group was 60-65%, and 40% in the ruptured group. No patient died in the ruptured group after one year, with the initial loss primarily due to a hospital mortality rate of 55%. The elective and urgent intact group had parallel curves with a yearly mortality rate between 4-7%. This agrees with reports of DeBakey,⁷ Szilagyi,³¹ and Key.²⁰

Ability to demonstrate an improved survival in the electively resected group requires comparison with a base-line mortality rate for the non-operated aneurysm group. Estes reported unoperated aneurysms had an 18% 5-year survival with a 66% incidence of rupture.¹⁴ In later reports by Szilagyi, the non-operated group had a 16% and 22% survival.^{31,32} However, reports by Schatz et al. and Wolfe estimate this 5-year survival at 30-40% with a 44% incidence of rupture.^{28,37} The Estes series was criticized for the high percentage of large pulsatile aneurysms, inclusion of ruptured aneurysms, and significant number of patients lost to followup. The experience of Schatz et al. does not include reasons for individual patient exclusion and has a high incidence of small (less than 7 cm) asymptomatic aneurysms (74%) representing a low-risk group. However, despite which survival figure (18% or 30-40%) is representative, the 60-65% 5-year survival in our series and others demonstrates a definite superiority of the surgically-treated group.^{7,31}

Late deaths in the elective group are primarily related to other manifestations of atherosclerosis (Table 5). The major cause of death was myocardial infarction in 41%,

cancer in 23% and stroke in 2% of patients. Similar results are seen in other areas of peripheral vascular disease. A group of patients who underwent carotid endarterectomies had a 66% 5-year survival rate, while those undergoing femoralpopliteal bypass grafting had a 52% 5-year survival.^{9,10} Late deaths in both groups were secondary to MIs and stroke in 30-35% of patients followed for 5-years.

The present series demonstrates a significant decrease in operative mortality rates and improved long-term survival of patients following aortic aneurysm resection. With experience and knowledge at its current level, patients with ruptured aneurysms now have a 55% chance of recovering. Those patients undergoing elective resections have less than a 7% mortality rate. Patients having urgent resections for increasingly symptomatic palpable aneurysms have a mortality rate similar to the elective group, and it is recommended that elective aneurysm resection be carried out on all patients who do not have significant medical contraindications.

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Pathologic Pulmonary Changes in Hemorrhagic Shock

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Fifty-seven dogs were subjected to hemorrhagic hypotension by a variety of protocols. Histologic pulmonary changes were studied using the light microscope. Of these 57 dogs, 21 had no demonstrable lesions, 8 had minimal changes, and 28 had moderate or severe lesions, all of a focal nature. No correlation was found between the presence of lesions and mean systemic arterial pressure during shock, the duration of the hemorrhagic period, the fate of the animal, preoperative hematocrits and blood volumes, mean postreinfusion arterial pressure, whether the animals were mongrels or purebred beagles, whether they were awake or sedated, whether they breathed spontaneously or were artificially ventilated, whether they had undergone previous splenectomy or not, whether hilar stripping was performed or not, and finally, whether blood was reinfused after hemorrhage or not. Thus we conclude that multiple factors may exert a harmful effect on the lung in hemorrhagic shock, and that shock probably makes the lungs more vulnerable to other injurious agents rather than there being one single pathogenetic mechanism for the pulmonary damage. The term "adult respiratory distress syndrome" rather than "shock lung" is best used for the human clinical entity since it implies a complex etiology rather than a discrete pulmonary lesion produced by a single pathogenetic mechanism.

PULMONARY damage has become increasingly important after shock, trauma, and operation. In attempting to define this damage, the term "shock lung" has been employed with increasing frequency and considerable imprecision.

Patients presumed to have this syndrome present with dyspnea, tachypnea, hypoxia and hypocarbia, and bilateral pulmonary infiltrates on roentgenogram. Pathologically the term has been inconsistently applied to lungs that are hypocreptant and have the consistency of liver on gross examination. Microscopically, the described picture has included focal or diffuse microatelectasis, congestion and dilatation of lung capillaries, alveolar hemorrhage, peribronchial and pericapillary interstitial

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edema, alveolar edema and hypertrophy of the alveolar lining cells with widening of the interalveolar septa, thromboemboli, and the formation of hyaline membranes. Lungs having this appearance have been observed in patients dying as a result of thoracic trauma,^{6,9} hemorrhagic hypotension^{5,7,12-14,16,17,21,23-25,33,37} sepsis,¹¹ postperfusion respiratory distress,^{29,37} viral pneumonia,³⁰ oxygen toxicity,²⁷ fluid overload,¹⁸ intravascular coagulation,¹⁸ fat emboli,² extensive burns,²⁸ and nonthoracic trauma.^{15,24}

There are many good laboratory investigations of the physiological and hemodynamic changes in shocked animals,^{10,12,17,19,31-35,37,40} and many clinical studies of patients with pulmonary insufficiency have been reported.^{1,4,5,15,20,21,24,27} However, there are few studies which have focused critically on the lesions that develop in the lungs as a result of uncomplicated hypovolemic hypotension.

The present work was therefore undertaken to define carefully the pulmonary lesions associated with uncomplicated hemorrhagic hypotension and to determine the importance of some proposed pathogenetic factors.

Methods

Seven groups of dogs were managed as follows:

Group I—Controls. This group consisted of 11 mongrel dogs of various weights. The dogs were anesthetized lightly with pentobarbital and ventilated with room air delivered through a cuffed endotracheal tube by a fixed volume respirator. Periodic hyperinflations were carried out to replace the normal sigh. Each dog was given 2 mg/kg of heparin intravenously. A left thoracotomy was performed, and small polyethylene catheters were placed in the pulmonary artery, pulmonary vein, left atrium, and femoral artery for measurement of pressure using strain

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gauge transducers. Cardiac output or pulmonary blood flow was determined by the indocyanine green dye dilution method with injection into the pulmonary artery and withdrawal from the femoral artery. Pulmonary vascular resistance was calculated according to the formula $\frac{PA-LA}{flow}$ where PA and LA represent the mean pulmonary artery and left atrial pressures in mm Hg, and flow represents pulmonary blood flow in liters per min. The dogs were sacrificed and autopsied after 4 hours.

Group II—Bled and Reinfused. This group consisted of 9 mongrel dogs of various weights. The dogs were anesthetized, ventilated, cannulated, and given heparin as in Group I. The animals were then bled slowly from the femoral artery into a closed plastic reservoir until a mean arterial blood pressure of 40-50 mm Hg was achieved. This degree of hypotension was maintained for 2 hours by draining blood from the dog or infusing blood from the reservoir. After the hypotensive period, the shed blood was reinfused. The animals were sacrificed and autopsied 2 hours after completion of the reinfusion.

Group III—Bled and Not Reinfused. This group consisted of 12 mongrel dogs of various weights. All were anesthetized, ventilated, cannulated, and given heparin as in Group I. The animals were bled and the hypotensive period maintained for two hours. The shed blood was not reinfused, and the dogs were sacrificed and autopsied at the termination of the two-hour hypotensive period.

Group IV—Bled and Reinfused, Awake Without Splenectomy. This group consisted of 14 purebred beagle dogs of approximately the same weights. They had been previously trained to lie quietly on the operating table. Although these dogs were gently restrained, they were not anesthetized, nor were thoracotomies performed. Each dog was given 50 mg of heparin intravenously prior to cannulation of the femoral artery and vein. A period of one hour of acclimatization to the operating table preceded each experiment. To achieve a mean arterial blood pressure of 40-45 mm Hg, blood was withdrawn over a 10-minute period from the femoral artery into a plastic syringe. After completion of the blood letting, an additional 25 mg of heparin were given to the dog, and 20 mg of heparin were added to each 100 ml of shed blood. This degree of hypotension was sustained for 1½-3 hours (11 dogs were hypotensive for the full 3 hours) by either withdrawing blood from the dog or infusing blood from the syringe. The femoral artery blood pressure and the pressure in the right ventricle (PE 100 catheter inserted via the femoral vein) were continuously measured and recorded. At the termination of the hypotensive period, the shed blood was reinfused. Seven dogs died within 15 hours after reinfusion of the blood; all were autopsied. Eight dogs survived for 24 hours after reinfusion, at which time they were sacrificed and autopsied.

Group V—Bled and Reinfused, Awake With Splenectomy. This group consisted of 11 purebred beagle dogs of

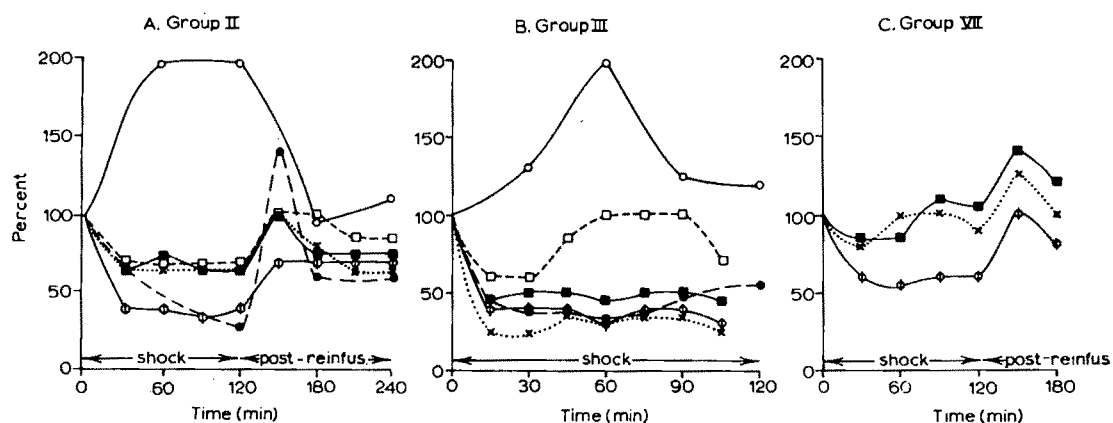
similar weight. Each had undergone splenectomy more than one month prior to the experiment. As in Group IV, all dogs were trained to be on the operating table before the experiment and were awake during the experiment. Shock was produced as described for Group IV animals (8 dogs were hypotensive for the full 3 hours). Six dogs died within 7 hours after reinfusion of the blood; all were autopsied. Five dogs survived for 24 hours after reinfusion, at which time they were sacrificed and autopsied.

Group VI—Bled and Reinfused: Early Sacrifice. This group consisted of 5 mongrel dogs of various weights. The dogs were anesthetized and ventilated as in Group I. Each dog was given 3 mg/kg of heparin. A left thoracotomy was performed and the animals cannulated as in Group I. The chest was then closed. Pressures in the left atrium, pulmonary artery, and femoral artery were determined using strain gauge pressure transducers. The dogs were bled and reinfused as in Group II. Four dogs died early in the shock period, and only one survived one hour after reinfusion of the blood, at which time it was sacrificed. All 5 dogs underwent autopsy.

Group VII—Bled and Reinfused with Left Lung Denervation. This group consisted of 6 mongrel dogs of various weights. The dogs were prepared similarly to those in Group VI. In addition to a left thoracotomy, the left pulmonary artery and left half of the left atrium were completely stripped of areolar and adventitial tissue. The left mainstem bronchus and accompanying nerves, blood vessels, and loose connective tissue were transected completely and the bronchus reanastomosed by previously described methods.³⁸ The chest was then closed with waterseal drainage. Pressures in the left atrium, pulmonary artery, and femoral artery were determined. The dogs were then made hypotensive using the same procedure as described for Group VI. After the hypotensive period the shed blood was reinfused, and one hour later the dogs were sacrificed and autopsied.

At the time of autopsy in all groups, all viscera were examined for the presence of grossly visible lesions. Special attention was paid to the lungs, and significant lesions were graded with respect to severity and photographed. Histologic sections were made of all organs, and multiple representative sections were made of each lung from each animal. Aliquots of tissue were fixed in 10% formalin, embedded in paraffin, sectioned at 7 μ , and stained with hematoxylin and eosin. The Lendrum stain for fibrin and other special stains were used when indicated. Histological sections of the lungs were examined to determine the presence or absence of the following lesions: edema, focal hyperemia, diffuse hyperemia, perivascular hemorrhage, intra-alveolar hemorrhage, and intrabronchial hemorrhage. A search for microemboli and leucocyte aggregates was also made. The overall severity of all histological lesions was evaluated and graded on a scale of 0 to 4+.

FIG. 1. Typical hemodynamic changes for animals in Groups II, III, and VII. ○—○ represents pulmonary vascular resistance, □—□ is pulmonary venous pressure, ■—■ is pulmonary artery pressure, ∅—∅ is femoral artery pressure, x—x is left atrial pressure, and ●—● is cardiac output. All values are expressed as percent of the control value. Group II animals were bled and reinfused, Group III were bled and not reinfused, and Group VII were dogs that were bled and reinfused after denervation of the left lung.



In Groups IV and V, red cell volume, plasma volume, and blood volumes were measured using a triple isotope technique, and conclusions were reached relating to transcapillary fluid shifts and sequestration of red cells. The details of this study have been reported elsewhere.¹⁰

Results

Typical hemodynamic changes for animals in Groups II, III, and VII are shown in Figs. 1A-C. In Group II, dogs were bled for two hours, then reinfused. During the shock period, pressures in the pulmonary veins, pulmonary artery, and left atrium decreased along with the femoral artery pressure. In the period after reinfusion, all 3 tended to rise. The left atrial pressure seldom rose above control values. The pulmonary venous pressure usually paralleled and was slightly higher than the left atrial pressure, but was considerably lower than the pulmonary artery pressure. The latter usually showed a considerable increase with reinfusion with a return to control values and then gradually declined. The cardiac output fell with hemorrhage and increased with reinfusion, often to levels above control values. Thereafter, the cardiac output gradually declined. The pulmonary vascular resistance increased dramatically during hemorrhage and usually remained elevated after reinfusion, although in some instances it gradually declined after reinfusion.

Group III dogs were bled but not reinfused. The pattern of all values tended to remain below control levels except for pulmonary vascular resistance which remained persistently elevated. The only significant difference seemed to be that the pulmonary venous pressure had a greater percentage increase during the shock period than the pulmonary artery or left atrial pressures.

Group VII dogs were bled and reinfused after left hilar stripping. Values in these dogs were similar to those in Group II (Fig. 1C).

The histologic findings in Groups II, III, IV, V, and VII are shown in Table 1. No lesions were noted in Group I, the control group, or in Group VI, and detailed findings are therefore not shown in Table 1. All other

TABLE 1. Histologic Changes in Individual Dogs

Hyperemia			Hemorrhage			Overall Grade
Edema	Diffuse	Focal	Peri-vascular	Intra-alveolar	Intra-bronchial	
<i>A. Group II</i>						
0	0	0	0	0	0	0
0	0	0	+	0	0	2+
0	0	0	0	0	0	0
0	0	0	0	0	0	1+
+	+	+	+	+	+	4+
0	+	+	+	+	+	4+
0	+	+	+	+	0	4+
0	+	+	0	+	+	4+
0	0	0	0	+	0	2+
<i>B. Group III</i>						
0	0	+	+	0	0	2+
0	0	0	0	0	+	1+
+	0	0	0	+	0	2+
+	0	+	0	0	0	1+
+	+	+	+	+	0	4+
0	+	0	0	+	+	3+
0	0	+	+	+	+	4+
0	0	+	0	+	+	3+
0	0	+	0	+	+	3+
+	+	+	0	0	+	3+
0	0	+	+	+	+	4+
0	0	+	+	+	0	3+
<i>C. Group IV</i>						
0	0	0	0	0	+	1+
0	+	0	0	+	0	3+
0	0	0	0	0	+	0
0	0	0	0	0	+	1+
0	0	0	0	0	0	0
0	+	0	0	0	0	2+
+	+	0	0	0	0	2+
0	0	0	0	0	0	0
0	0	+	+	+	0	3+
+	0	+	+	0	0	3+
0	0	0	0	0	0	0
0	0	+	+	+	0	3+
0	0	+	+	0	+	3+
0	0	0	0	0	0	0

TABLE 1. (Continued)

<u>Hyperemia</u>			<u>Hemorrhage</u>			Overall Grade
Edema	Diffuse	Focal	Peri-vascular	Intra-alveolar	Intra-bronchial	
<u>D. Group V</u>						
+	0	+	0	+	+	3+
0	+	0	0	+	0	2+
0	0	+	0	0	0	1+
0	0	0	0	0	0	0
0	0	+	+	0	0	2+
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	+	+	0	0	2+
0	0	0	0	0	0	0
0	0	0	0	0	0	0
<u>E. Group VII</u>						
0	0	0	0	0	0	0
0	0	0	0	0	0	0
+	+	0	0	+	0	3+
0	0	0	0	0	0	0
0	0	+	0	0	0	1+
0	0	0	0	0	0	0

groups had pulmonary lesions, but no group consistently had severe (4+ and 3+) or moderate (2+) lesions. There was a random scattering of lesions in all groups, and instances where no lesions could be identified occurred in all groups. No microembolic or leucocyte aggregates were found. In Group VII, there was no difference in the histologic findings between the right and left lungs.

The presence or absence of these lesions did not correlate with the mean systemic arterial pressure during shock, the fate of the animal (whether it survived 24 hours or died early), or the mean arterial pressure after reinfusion. Despite the fact that the hypovolemic period varied from 90 to 180 minutes, it was also impossible to define a consistent relationship between observed lesions and the duration of the hypovolemic periods. In Groups IV and V, the animal with the lowest hematocrit (29.5%) and the one with the lowest blood volume (784 ml) had no lesions. On the other hand, some animals with high hematocrits and blood volumes had lesions. Most animals had hematocrits greater than 45%, and in these there was a random scattering of lesions. Similarly, there was no correlation between the presence of pulmonary lesions and whether the animals were purebred beagles or mongrels, whether they were awake or sedated, whether they breathed spontaneously or were artificially ventilated, whether they had undergone previous splenectomy or not, whether hilar stripping was performed or not, and finally whether blood was reinfused after hemorrhage or not.

Discussion

Of the 57 dogs that were studied in the experimental

groups, 21 had no demonstrable lesions, 8 had minimal (1+) changes, and 28 had moderate (2+) or severe (3+ or 4+) lesions. Thus, lesions were inconsistently present from animal to animal, and there was no uniformity within different groups studied. Lesions when present were predominantly of a focal nature in individual sections. Consistent moderate or severe intra-alveolar and/or interstitial edema, intra-alveolar and perivascular hemorrhage, hypertrophy of alveolar lining cells, or the presence of hyaline membranes were not observed. From these results, we concluded that there is no characteristic or pathognomonic pulmonary lesion associated with or resulting from uncomplicated hypovolemic hypotension. Thus, the terms "shock lung" and its supposed typical pathologic lesion "congestive atelectasis," which is defined as capillary congestion, atelectasis and hemorrhage, appear to be inappropriate as pathologic diagnoses.

Older studies by other workers support these conclusions. Wiggers and his colleagues³⁹ found that 2 of 6 dogs that died in shock had severe bronchopneumonia. Of 10 other dogs that survived comparable levels of shock, all had only occasional small hemorrhagic infarcts in their lungs. Moon²³ distinguished the pathologic pulmonary changes produced by "shock" from those produced by hypovolemic hypotension. In the latter, he believed only ischemic changes occurred; whereas, in the former, petechiae and congestion were present. Eaton¹³ studied³⁴ animals subjected to hemorrhagic shock and 4 controls and found some edema, hemorrhage, and capillary congestion in the controls as well as in the shocked animals, although he believed that there was a definite increase in all these changes in the shocked dogs. Roundthwaite and his colleagues³² also described variable changes in 16 dogs subjected to hemorrhagic shock. Jenkins and his associates¹⁸ produced so called "congestive atelectasis" in dogs by rapid infusion of physiological saline. These authors noted that the lungs barely floated and had a liver-like appearance which disappeared on inflation. Microscopic examination prior to inflation showed capillary congestion, intra-alveolar hemorrhage, atelectasis, and edema. However, he found that the areas affected by "congestive atelectasis" disappeared with inflation of the lung. From this review it seems that the older literature describes a variety of lesions that occur in shock and which are inconsistently present. These include bronchopneumonia, hemorrhagic infarcts, congestion, petechiae, ischemia, and atelectasis.

On the other hand, the more recent literature implies or actually states that hemorrhagic shock routinely produces a pathognomonic pulmonary picture. Sealy and his colleagues, in two different studies,^{33,40} noted that 12 of 24 shocked dogs in one series, and 8 of 10 in another series had pulmonary lesions. Barkett,³ indicated that 27 dogs that had been subjected to hemorrhagic shock had

lung changes ranging from minimal pulmonary congestion to massive congestive atelectasis. Keller and his coworkers¹⁹ produced lesions of varying severity in all of 8 dogs subjected to hemorrhagic shock. Henry and his associates¹⁷ implied that all of 38 animals had lesions, and Cook and Webb¹² suggested that 23 of their dogs subjected to hemorrhagic shock developed pulmonary lesions. Moss²⁶ and Sugg and his colleagues³⁵ noted that hemorrhagic shock uniformly produced significant pulmonary lesions in the normal right lung of dogs while their previously reimplanted and thus denervated left lungs remained free of such lesions. Bryant and his associates⁷ implied that all 30 of their dogs had lesions. They believed that those on respirators had less severe lesions, and those with less severe shock had fewer lesions.

Our work does not support the conclusion that hemorrhagic shock routinely produces pathognomonic pulmonary lesions. The lung seems to respond inconsistently to shock with only minor focal changes of edema and hemorrhage, and these lesions are usually reversible if the animal survives. Our findings are also supported by additional recent work. Buckberg and his coworkers⁸ found no pulmonary lesions in baboons subjected to shock. Proctor and his associates³¹ and Einheber and Cerilli¹⁴ showed minimal inconsistent pulmonary changes after shock in primates, and Silberschmid and his colleagues³⁴ found no visible damage in the lungs of dogs in hemorrhagic shock. Meyers and his coinvestigators²² in a study of 30 dogs subjected to hemorrhagic shock noted no specific morphological lesion in the lungs up to 5 days after resuscitation.

It is difficult to understand why there is such a wide variation in results using similar methods of producing hemorrhagic shock. The differences might be due to the methods of handling the lungs and preparing them for microscopic study, or to the presence of preexisting acute pulmonary diseases in the dogs. In addition, most studies have been concerned with functional changes, and the lesions noted were usually not interpreted or quantitated by pathologists and many have been in error.

In man also, there is at present no direct evidence that proves unequivocally that specific pulmonary damage occurs as a result of shock, or that there is a pathologically diagnosable entity of "shock lung." Teplitz stated that most of the clinical cases shown and discussed at the Washington conference on post-traumatic pulmonary insufficiency represented non-specific pulmonary edema and congestion rather than any specific lesion.³⁶ Martin and others, studying 100 autopsies of soldiers dying of trauma and shock, found only one of 34 examined microscopically to have lesions which could be classified as "congestive atelectasis" in the lungs, whereas 68 of 100 had pulmonary edema and 14 of 100 autopsies had hyaline membranes.²¹

Thus, the present evidence based on light microscopy

supports the following conclusions: The lung has a limited number of ways to respond to injury. The existence of hemorrhagic shock probably makes the lungs more vulnerable to other injurious agents rather than there being one single pathogenetic mechanism of lung damage in hemorrhagic shock. These multiple other factors which can exert a harmful effect on the lung in shock include fluid overload, microemboli in transfused blood, systemic and pulmonary infection, congestive heart failure, aspiration, oxygen toxicity, thoracic and pulmonary trauma, retained secretions and atelectasis, fat emboli, pulmonary emboli, and others.

From a clinical and therapeutic point of view, we therefore would advocate that the term "shock lung" be replaced with Ashbaugh's term "adult respiratory distress syndrome."¹¹ This identifies a clinical presentation, and says nothing about the pathologic lesions in the lung or the pathogenetic mechanisms involved. In patients who are at risk to develop this entity, an effort should be made to minimize the influence of these other factors that may injure the lung.

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Volvulus of the Cecum

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A series of 37 patients with cecal volvulus treated at three different Swedish hospitals during the years 1952-1973 is presented. The symptoms, physical findings and radiologic features are presented. The associated factors found at operation are described and their possible role in provoking torsion is discussed. In 5 patients the diagnosis did not become clear until autopsy. Thirty-two patients were subjected to operation. The operation consisted of detorsion in 11 cases, cecopexy in 10, cecostomy in 3 and cecopexy plus cecostomy in 3 patients. The remaining 5 patients were subjected to right sided hemicolectomy. Of these 5 patients one died postoperatively. There were 6 postoperative deaths after other forms of surgery. The survivors were followed, and the mean followup period was 7 years. There was recurrence in only two patients, both treated with cecopexy. The controversial problem of the preferable surgical method is discussed and a review is given of results in series reported during the last 15 years. It was concluded that when the bowel is viable, cecopexy is the treatment of choice while hemicolectomy should be performed in cases with gangrene.

VOLVULUS of the cecum is an axial twist or a folding of the bowel upon its mesentery. This results in acute intestinal obstruction which may or may not be complicated by occlusion of the mesenteric vessels. The condition was first described by Rokitsky¹⁵ in 1837 and for reasons which are not fully understood it seems to be more common in Scandinavia and Eastern European countries than in Western Europe and the United States. There are a number of important differences between volvulus of the cecum and the much more common volvulus of the sigmoid colon. These differences stem from localization and mobility of these two parts of the colon and they are reflected by differences in symptomatology, radiology and prognosis. Although its distinctive characteristics are perhaps not always clarified in reviews of the subject, colonic volvulus also stands apart from a therapeutical point of view. It is the purpose of the present paper to analyze a series of 37 patients treated in

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three different Swedish hospitals for volvulus of the colon. The emphasis of this analysis is on the controversial subject of surgical treatment. We reasoned that the analysis of such a large series might have a better chance for giving guidelines for therapy than the comparatively small series hitherto reported.

Patient Series

The series comprises all 37 patients with cecal volvulus treated during the 20-year period 1952-1973 at the surgical departments of the hospitals of Umeå (12 patients), Östersund (20 patients) and Kristianstad (5 patients). There were 20 females and 17 males, the mean age of the female patients being 63 years (range 14-89 years) and that of the males 64 years (range 10-91 years).

Symptoms and Signs

In all except 3 patients there was a history of abdominal pain. As a rule the pain was severe and colicky with acute onset. Abdominal distension was noted in only 40 per cent of the patients (14 of 37). Nausea and vomiting were present in the majority (20 of 37). The length of the history before the patients sought treatment varied considerably i.e. from 3 hours to 10 days with a mean of 2 days. Three patients gave a history of previous attacks of similar pains which had subsided without surgical intervention or other treatment.

In the great majority of our patients (30 of 37) the abdomen was distended and tympanitic. Signs of acute peritonitis with wide-spread abdominal tenderness and rigidity of the entire abdominal wall were present in one patient. In this patient a gangrenous cecum was found at operation to have perforated, giving rise to a general peritonitis. High pitched bowel sounds were audible in three of the 37 patients. In only 7 patients the tempera-

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TABLE 1. Summary of 37 Patients with Volvulus of the Cecum

Pat No	Sex, Age	Duration of Illness	Previous Abdominal Surgery	Operative findings other than cecal volvulus	Operative procedure	Result
1	F, 55	24 hrs	None	Mesenterium commune Cecal gangrene	Cecostomy	Died postop Dy 1
2	M, 72	10 dys	None	Mesenterium commune	Cecopexy appen- dectomy	Died postop Dy 9
3	F, 61	2 dys	Cecopexy 8 years earlier	None	Cecopexy	No recurrence 14 yrs later
4	M, 91	2 dys	Appendectomy	No operation	Autopsy finding	—
5	M, 83	24 hrs	None	No operation	Autopsy finding	—
6	F, 74	2 dys	None	No operation	Autopsy finding	—
7	F, 19	2 dys	Appendectomy, mobilization of cecum	None	Cecopexy	No recurrence 1 yr later
8	F, 66	5 dys	Incarc. umbilical hernia 29 days earlier	—	Autopsy finding	—
9	F, 76	24 hrs	None	None	Cecopexy + lysis of adhesions	No recurrence 10 yrs later
10	M, 87	4 dys	None	None	Detorsion	Died postop Dy 6 (pneu- monia)
11	F, 68	36 hrs	None	None	Detorsion	Died 4 mon postop from pneumonia. No recurrence.
12	F, 67	24 hrs	None	None	Cecopexy	No recurrence 2 yrs later
13	F, 74	2 dys	None	None	Right colectomy	Died postop Dy 4
14	M, 41	24 hrs	None	None	Detorsion + lysis of adhesions	No recurrence 21 yrs later
15	M, 31	3 hrs	None	None	Detorsion	No recurrence 9 yrs later
16	M, 54	30 hrs	Appendectomy	None	Cecopexy + lysis of adhesions	No recurrence 5 yrs later
17	M, 70	24 hrs	None	Cecal gangrene	Right colectomy	Good
18	F, 81	4 dys	None	Cecal gangrene.	Right colectomy	Died postop Dy 15
19	M, 16	9 hrs	None	None	Cecopexy + cecos- tomy	No recurrence 17 yrs later
20	F, 89	12 hrs	Cholecystectomy	None	Cecopexy	Died 1 yr later No recurrence
21	F, 71	2 dys	Nephrectomy	Sigmoidal carcinoma	Cecopexy + cecos- tomy	Died 9 mon later No recurrence
22	F, 81	2 dys	Hernia in cicatrice 1 day earlier, appendectomy	—	Autopsy finding	—
23	F, 86	24 hrs	None	None	Detorsion	Died postop Dy 7 (Insuff. cordis)
24	F, 65	24 hrs	Appendectomy. Op for umbili- cal hernia	None	Cecopexy	Recurrence 10 yrs later Reop. right colectomy
25	M, 74	24 hrs	None	Cecal gangrene with perforation	I Exteriorization II Right colectomy	Good
26	M, 53	5 dys	None	None	Cecopexy + cecos- tomy	No recurrence 3 yrs later
27	F, 57	3 dys	Cholecystectomy, gastric resection	None	Cecostomy	No recurrence 11 yrs later
28	F, 75	2 dys	Appendectomy + myomectomy	None	Cecopexy	Recurrence 2 yrs, 8 mon later. Reop: Cecopexy, no recurrence 1 yr later
29	M, 91	24 hrs	None	Rectal carcinoma	Cecostomy	No recurrence Died 1 yr later
30	M, 89	2 dys	Transabdominal prostatectomy	None	Appendectomy Detorsion	Died postop Dy 18
31	F, 26	24 hrs	None	None	Detorsion + Appendectomy	No recurrence 6 yrs later
32	F, 14	30 hrs	None	None	Detorsion Appendectomy	No recurrence 10 yrs later
33	M, 75	24 hrs	None	Cecal gangrene	Right colectomy	Good
34	M, 83	15 hrs	None	None	Reduction + lysis of adhesions + appendectomy	No recurrence 1 yr later
35	F, 42	24 hrs	None	None	Cecopexy	No recurrence 7 yrs later
36	M, 69	24 hrs	None	Mesenterium commune	Reduction only	Died postop Dy 5
37	M, 10	5 days	None	Mesenterium commune	Reduction + lysis of adhesions	No recurrence 13 yrs later

ture was elevated over 38 C. Finally, although leukocytosis was conspicuously absent in many patients, the mean white blood cell count was elevated, 10,900 per mm³ with a range from 4,200-20,300.

Radiological Findings

A plain abdominal roentgenogram had been made in 29 of our 37 patients while the radiological examination had been supplemented with a barium enema in 14 cases. Characteristically a plain x-ray film showed a dilated air filled colon in the right part of the abdomen while at the barium enema the cecum was not visualized and there was a "bird's beak" deformity in the right lower quadrant. Such characteristic signs were, however, present in only 10 of the 29 radiologically investigated cases. In one case—the one with general peritonitis due to perforation of a gangrenous caecum—free gas was found to be present. In 10 cases the radiological examination led to a diagnosis of large bowel obstruction of unknown origin and in the remaining 18 cases a diagnosis of small bowel obstruction was made.

Associated Factors

Twelve patients had previously been subjected to abdominal surgery. A survey of these previous operations is given in Table 1. As seen in Table 1 most of these operations consisted of appendectomy or cholecystectomy i.e. operations which most likely were not related to the ensuing cecal torsion. In a few patients there was a possible causal connexion and these case histories warrant special comment:

Case 3. A 61-year-old woman had had surgery for a cecal volvulus 8 years before. Cecopexy had been performed with catgut as suture material. She was again admitted 8 years later with similar symptoms. Cecopexy was again performed but this time silk was used. Afterwards the patient was free from abdominal symptoms until her death from an unrelated cause 14 years later.

Case 7. A 19-year-old girl had been subjected to appendectomy 7 years previously. Delivering the appendix had been unusually difficult and the surgeon had been forced to mobilize part of the cecum. Volvulus of the colon developed 7 years later.

Case 8. A 66-year-old woman underwent surgery for an incarcerated umbilical hernia. The postoperative course was complicated by infection of the wound. An abscess formed and was drained but in spite of antibiotics and intensive care her condition deteriorated and she died on the 29th postoperative day. Autopsy revealed as the probable cause of death a cecal volvulus which had gone undiagnosed during life. The abscess was found to have obstructed the transverse colon.

Case 22. An 81-year-old female had been appendectomized in early life. She had later developed an incisional hernia and was admitted with signs of incarceration

of this hernia and underwent immediate surgery. The patient died on the second postoperative day and at autopsy a cecal volvulus was found. Apart from these 4 patients in whom there is a reasonably certain connexion between an abdominal operation and the development of cecum volvulus there were two patients in whom the volvulus may have been related to a distal obstructing lesion. In one case such a lesion consisted of a rectal cancer and in another the lesion was cancer of the sigmoid colon. Finally, it is worthy of note that a commune mesentery was found in no less than 4 patients.

Treatment

As seen in Table I operation was performed in 32 of the 37 patients. In the remaining 5 cases the diagnosis was made at autopsy. Three of these latter patients (cases 4, 5 and 6) died soon after admission to hospital and before surgery could be carried out. In the two other patients (cases 8 and 22) volvulus of the cecum developed postoperatively, in case 8 after an operation for incarcerated umbilical hernia and in case 22 after an operation for incarcerated incisional hernia. Table 1 shows the operative procedures performed in the remaining 32 patients. Detorsion without fixation of the cecum was performed in 11 patients. Detorsion with ensuing cecopexy was done in 10 patients. In the majority of these patients lateral wall cecopexy was carried out. Cecopexy with cecostomy was done in 3 patients. Finally right hemicolectomy with end to end ileotransverse colostomy was performed in 5 patients, in 4 of whom the cecum was considered non-viable.

Postoperative Course

One of the 5 patients subjected to right hemicolectomy died postoperatively while there were 6 postoperative deaths among the 27 patients who had undergone other forms of surgery. These patients were followed up for a mean period of 7 years. There was recurrence of the volvulus in two patients (cases 24 and 28), both of whom had undergone cecopexy.

Discussion

In the present series women predominated; there were 20 female as compared with 17 male patients. A similar predominance of women was found in most other series with the exception of the one by Gardiner⁶ who found cecal volvulus to be more common in men. The mean age of our patients was just over 63 years which is comparable to that reported by Wolf & Wilson,¹⁹ Krippaehne et al.⁸ and Smith and Goodwin.¹⁷ The mean age is, however, markedly higher than that in most other series.^{1,4,10} It is also clearly higher than that in another large Swedish series.¹² It should be pointed out that the majority of our patients (32 of 37) stem from two counties in the North of Sweden where due to an outflow of men and women in

the actively productive ages, old people are overrepresented. In other words the difference may be due to a difference in the population at risk.

Hypofixation of the cecum is a prerequisite for torsion and in accordance with other reports such a freely mobile cecum was found in all patients of this series. In 4 patients there was a commune mesentery. In one patient in our series the cecum had been mobilized in the course of a technically difficult appendectomy. Apart from this patient there were 5 others who had earlier been appendectomized and it is of course possible that also in the other 5 patients the operation had implied some mobilization of the cecum. On the other hand, it seems reasonable to expect a certain number of earlier appendectomies in any series of patients of this age and a causal connection between the operation and the later development of cecum volvulus can hardly be suspected. Apart from this, free mobility of the cecum seems to occur rather frequently. Wolfer et al.²⁰ found the cecum to be mobile in no less than 11% of their autopsy cases. In view of the relative rarity of cecum volvulus, hypofixation does not suffice as an explanation and it is clear that there must be other precipitating factors. In the search for such provoking factors much attention has been paid to the influence of a high residual diet. Such a coarse vegetable diet could explain the higher incidence in Eastern European countries.² But, in Scandinavia the incidence is also higher than in Western Europe and the United States while there are no marked dietary differences between these geographical regions. Overeating is sometimes also mentioned as an etiological factor.¹³ This was not a prominent feature in the present series and it could be suspected in only one patient who had eaten an unusually large quantity of raisins some hours prior to the development of symptoms.

Other provoking factors which have been discussed are left colonic obstructive lesions and adhesive bands secondary to previous operations. Ritvo et al.¹⁴ found colonic lesions distal to the site of the volvulus in no less than 50% of their cases. In other series the incidence is somewhat less high. For instance Krippaehne et al.⁸ reported distal obstruction in 8 of their 22 patients. In the present series the frequency of distal obstructing lesions was considerably lower. We found such lesions in only three of our 37 patients. In one case there was a cancer of the sigmoid colon, one patient had a rectal cancer and in the third patient the distal obstruction consisted of an abdominal abscess which constricted the transverse colon. As for the possible influence of adhesions after previous operations, the reported incidence of such operations differs widely. The highest incidence seems to have been reported by Dixon and Meyer,³ only two of their 12 patients had not had previous intra-abdominal operations. This is significantly more than in the present series in which only 12 of 37 patients had previously been

subjected to abdominal surgery. Other series hold an intermediate position e.g. in the series of Wolf and Wilson¹⁹ abdominal surgery had been performed earlier in 12 of 22 patients.

The frequency with which gangrene is reported in the different series does not vary as markedly. Feterson¹² reported gangrene in 3 of 11 patients and in the series of Krippaehne et al.⁸ and in that of Hinshaw et al.⁷ the incidence is about 30%. In the present series this incidence is somewhat, although not significantly, lower; we found gangrene of the cecum in 5 of our 37 patients. Clearly, the viability of the bowel is of the utmost importance for the operative procedure to be selected. Gangrene of the cecum calls for a hemicolectomy which was performed in 3 of these 5 patients or for a Mickulicz-type exteriorization which was done in one case. In the fifth patient the extent of gangrene was limited and in this case only a cecostomy was performed.

Although opinions differ on the choice of the operative procedure there is general agreement that surgery should be undertaken as soon as the patient's general condition permits. The greater the lapse of time between the onset of symptoms and the operation the greater is the mortality.⁷ The controversy regarding the proper surgical technic of correction of cecal volvulus concerns especially those cases in which the bowel is viable. On the one hand are the advocates of cecopexy which can be combined with cecostomy, on the other are those surgeons who also recommend an emergency right hemicolectomy for these cases. Resection as treatment for cecal volvulus when the bowel is viable was introduced by Melchior⁹ after he had experienced two recurrences following cecopexy. The danger of recurrence of the condition is still the main argument of the proponents of resection. Against this danger, which undoubtedly exists must be weighed the increased dangers connected with an emergency hemicolectomy without prior antibiotic therapy and performed in patients who more often than not are in a relatively poor general condition. It is our belief that when confronted with this problem the surgeon should choose the procedure with the least immediate risk, i.e. cecopexy. We base this opinion on the relative rarity of recurrence. A proper estimate of the frequency of recurrence cannot be gained on the basis of one individual series but only by a study of the combined experience as reported in the literature. Table 2 gives the incidence of recurrence in non-resected patients during the last 15 years. It shows that this incidence must be considered as low. It was less than 5% in this combined series in which there were a number of patients in whom fixation of the cecum was not even attempted but surgery had been limited to detorsion. In the present series with a mean followup period of 7 years, we observed only two cases of recurrence, although in 11 of our 27 non-resected patients surgery had been restricted to detorsion.

TABLE 2. Incidence of Recurrence in Different Series of Non-resected Patients with Cecal Volvulus.

Authors	No. of Patients and Type of Operation			Detorsion	Total	Died postop	Mean Followup period	Recurrences
	Ceco-pexi	Ceco-stomy	Ceco-pexi + stomy					
Bagley, et al. ¹	—	2	—	5	7	0	?	0
Sawyer, et al. ¹⁶	?	?	?	?	22	1	?	3
Wolf & Wilson ¹⁹	8	2	2	5	17	4	?	0
Krippaehne, et al. ⁸	2	8	—	5	15	8	?	0
Peterson ¹²	2	1	—	3	6	1	5 yr 8 mon	0
Dowling & Gunning ⁵	2	2	—	3	7	0	?	0
Smith & Goodwin ¹⁷	3	—	17	—	20	2	?	0
Present series	10	3	3	11	27	6	7 yrs	2
Total	27	18	22	32	121	22	—	5 (4%)

When the bowel is not viable the situation is of course totally different. In cases with a small area of focal gangrene, advantageously located, this area can sometimes be excised and a cecostomy tube can then be placed through the resulting defect. In our series cecostomy was performed in 3 patients. Apart from decompression of the intestine, fixation of the cecum is obtained by this simple procedure. It seems, however, that this form of fixation is not fully reliable as cases with recurrence have been described.^{11,18}

Finally, there are those cases in which gangrene is either more wide spread or not so advantageously located. In these cases the surgeon has no choice; resection consisting of right hemicolectomy with end-to-end ileo-transverse colostomy is to be preferred while in poor risk cases a Mickulicz type exteriorization could be tried.

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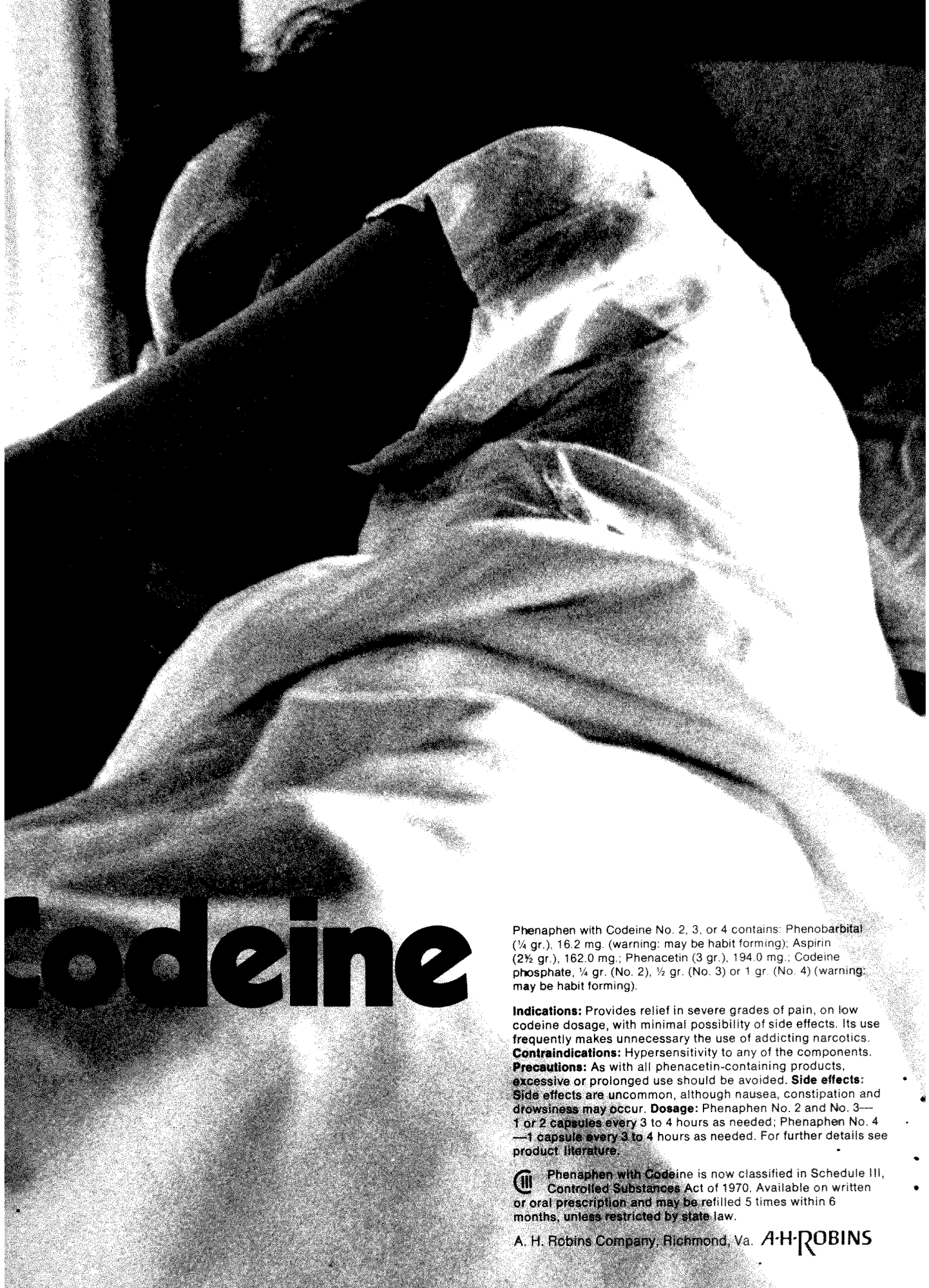
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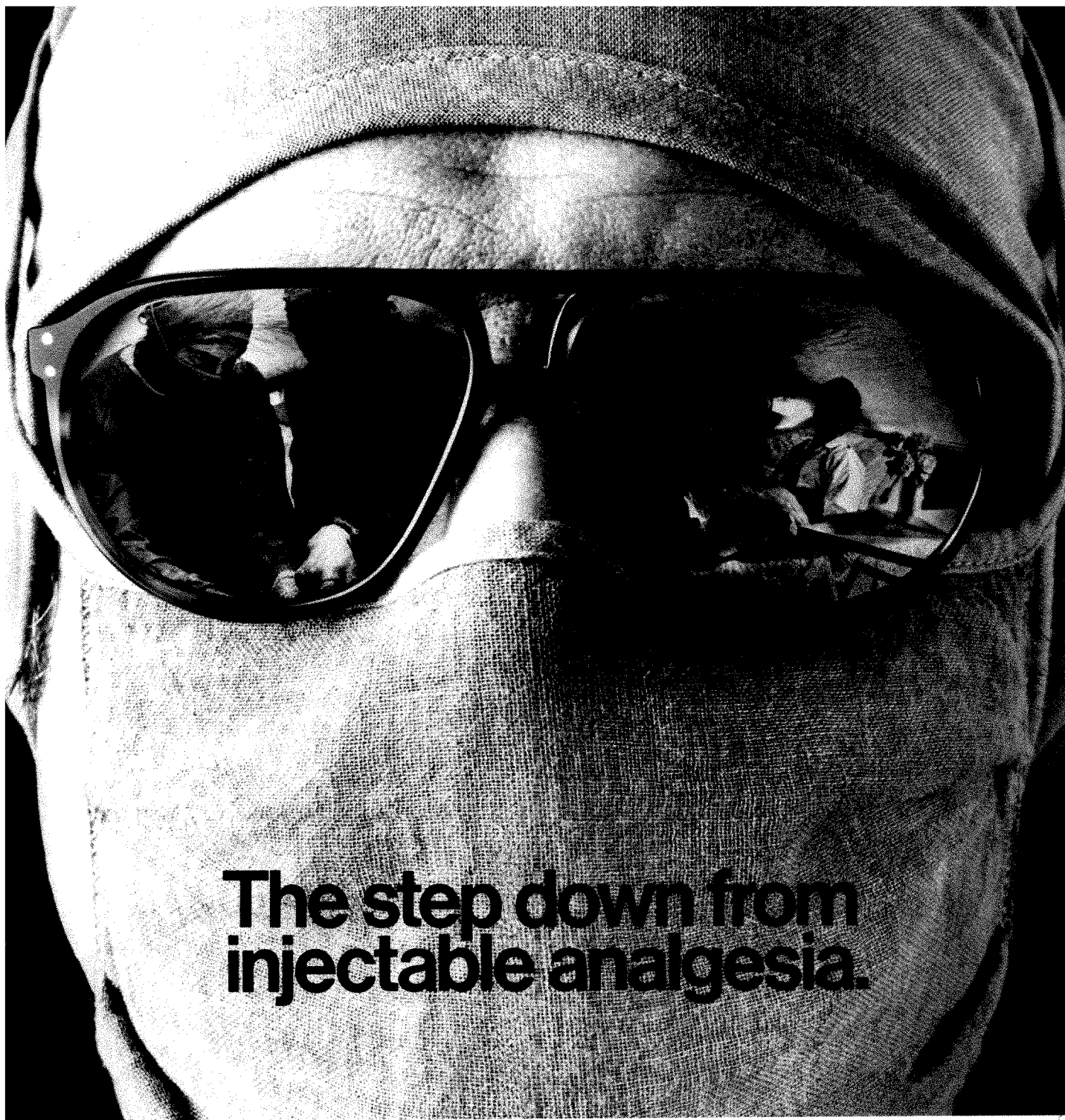
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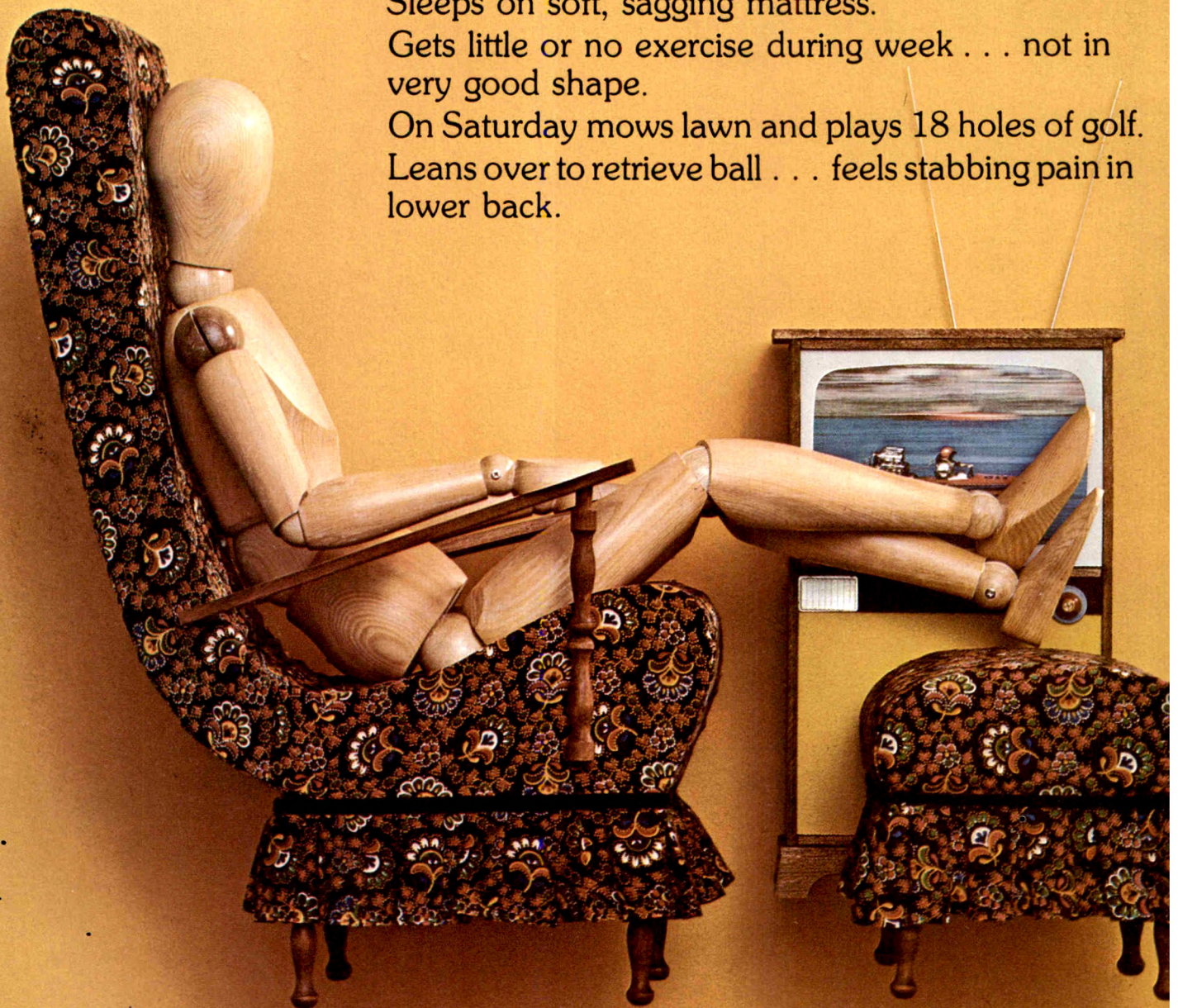
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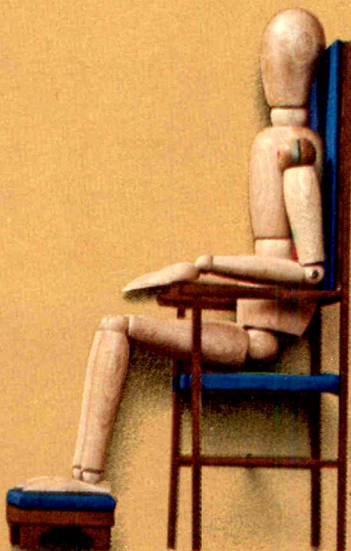
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Gets little or no exercise during week . . . not in
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On Saturday mows lawn and plays 18 holes of golf.
Leans over to retrieve ball . . . feels stabbing pain in
lower back.



the solution:



At work sit in straight chair with firm back . . . knees higher than hips. Prop feet on small footstool to elevate knees. Don't sit in over-stuffed furniture. Never sit long in one position . . . get up frequently and move around. Exercise regularly to strengthen abdominal and low-back muscles and help prevent weekend flare-ups. Avoid sudden spurts of vigorous physical activity. A back support can help relieve pain and fatigue.

to relieve discomforts associated with acute, painful musculoskeletal disorders...

ROBAXIN[®]-750

brand of

methocarbamol

750 mg. capsule-shaped tablets

Indications:

As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:

Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:

Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:

Safety and effectiveness in children below the age of 12 years have not been established.

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:

Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:

Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.

Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:

ROBAXIN[®] (methocarbamol) 500 mg.

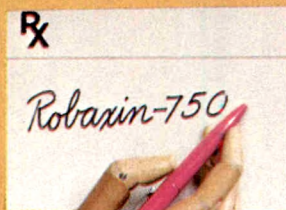
See package insert for full prescribing information.

the Robaxin Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood $\frac{1}{2}$ - $\frac{3}{4}$ " thick between mattress and box springs. The use of moist heat is often very beneficial.



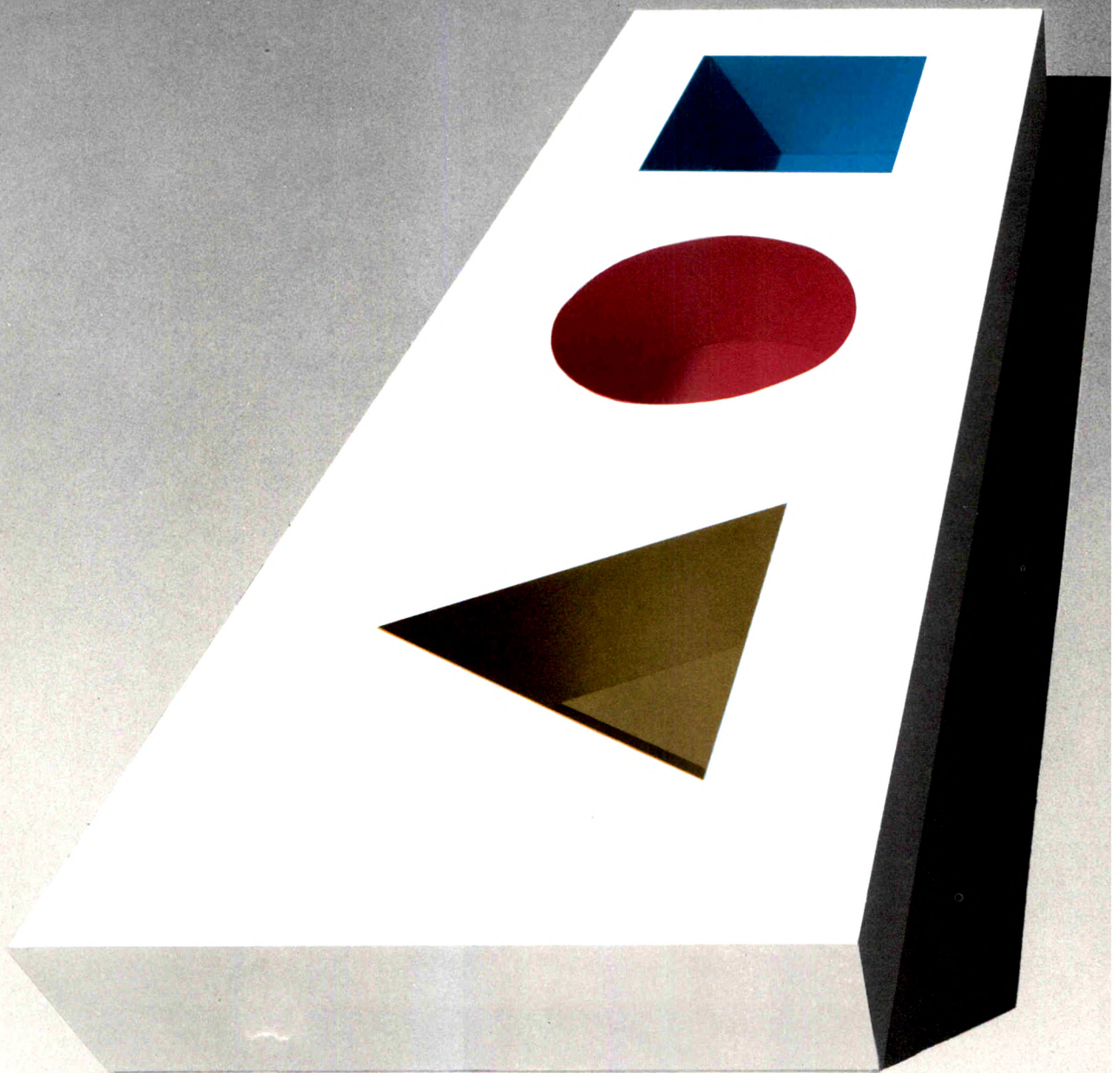
Robaxin-750 is often indicated to relieve the discomforts associated with acute, painful musculoskeletal disorders. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.



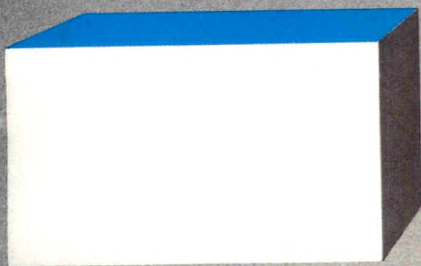
A. H. Robins Company, Richmond, Va. 23220

A-H-ROBINS

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Mead Johnson can fulfill their nutritional needs



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Ideally formulated to provide for the extra nutritional needs of the broad range of patients requiring an oral supplement or high protein diet in a convenient, well tolerated form.

An excellent tasting liquid dietary featuring high protein, low lactose, moderate osmolality and balanced levels of vitamins and minerals.

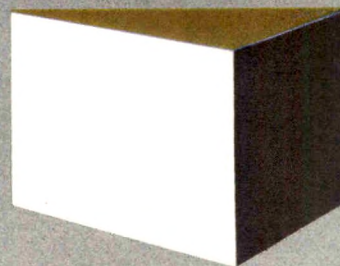


FLEXICAL[™]

Low-residue, Elemental Diet...

Ideally formulated to fulfill the specific nutritional needs of critically ill patients who require a diet with minimum digestive activity and low levels of fecal residue.

A balanced diet featuring unsurpassed protein quality in the form of protein hydrolysate plus free essential amino acids, simple carbohydrates, low sodium content, and MCT[®] Oil as a component of fat to ease digestion.



ISOCAL[™]

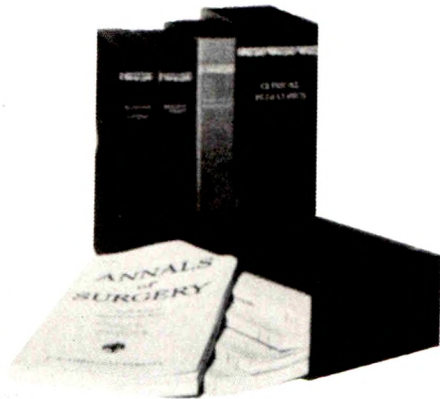
Standard Tube Feeding...

Ideally formulated to provide for the nutritional needs of most tube-fed patients.

Helps eliminate troublesome side effects, particularly diarrhea, because of its nearly isotonic nature and absence of lactose.

This ready-to-use liquid diet also features MCT[®] Oil as a component of fat to ease digestion, and 2000 Calories provide at least 100% of the U.S. RDA's for protein and essential vitamins and minerals.

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DARVOCET-N® 100

propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: Drug Dependence—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions.

[011375]

DARVON® COMPOUND-65

propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: Drug Dependence—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions.

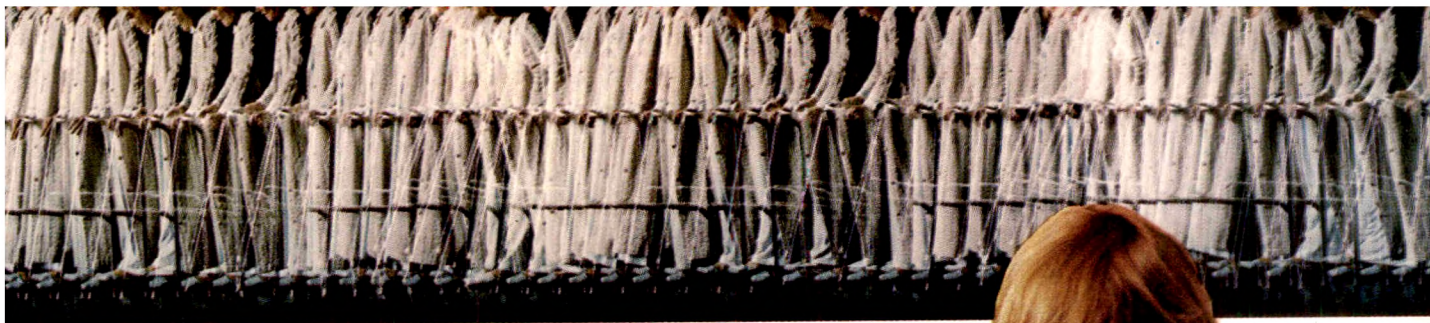
[011375]



Additional information available
to the profession on request.

Eli Lilly and Company, Inc.
Indianapolis, Indiana 46206

500390



Relief from her postsurgical pain

Darvocet-N[®]100

100 mg. propoxyphene napsylate and
650 mg. acetaminophen

contains no aspirin



Darvon[®] Compound-65

65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin

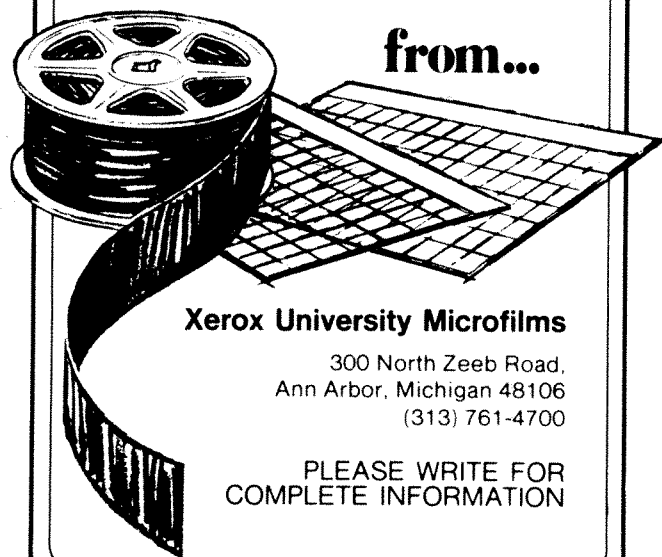


for mild to
moderate pain

See summary of prescribing information on adjoining page.

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Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Tigan is indicated for the control of nausea and vomiting.

CONTRAINDICATIONS: The injectable form of Tigan in children, the suppositories in premature or newborn infants, and use in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.

WARNINGS: Tigan may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. Reye's Syndrome has been associated with the use of Tigan and other drugs, including antiemetics, although their contribution, if any, to the cause and course of the disease hasn't been established. This syndrome is characterized by an abrupt onset shortly following a nonspecific febrile illness, with persistent severe vomiting, lethargy, irrational behavior, progressive encephalopathy leading to coma, convulsions and death.

Usage in Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or still-born pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.

PRECAUTIONS: During the course of acute febrile illness, encephalitis, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

HOW SUPPLIED: Ampuls, 2 ml, boxes of 10. Multiple Dose Vials, 20 ml. Thera-Ject™ (Disposable Syringes), 2 ml, boxes of 10.

Many things have changed in the operating room in 15 years...

but the Tigan effect hasn't.

(trimethobenzamide HCl)



When Tigan was introduced in 1959, nausea or vomiting was a frequent post-operative occurrence. Advances in surgical technique and anesthetic agents have reduced these incidences. However, when you need control of emesis and need it quickly, Tigan provides the necessary effectiveness with a relative lack of side effects.

Tigan has been used successfully with many different anesthetics and in all types of surgery without potentiating the anesthesia, delaying the awakening or altering the patient's vital signs (although a few instances of hypotension have been reported).

Beecham

laboratories, Bristol, Tennessee 37620

Tigan Injectable is intended for intramuscular administration only: the recommended adult dose—2 ml. (200 mg.) t.i.d. or q.i.d. (It is contraindicated in children)



For prompt control of nausea and vomiting

Tigan® Injectable

(trimethobenzamide HCl)

Please see adjoining page for Brief Summary

Quick Reference To Surgical Emergencies

Edited by Gerald W. Shaftan, M.D.
and Bernard Gardner, M.D.

This new manual, packed with clinical data in easy-to-use outline form, is designed for instant use in helping you evaluate the surgical emergency, make the diagnosis and carry out the indicated treatment.

Divided into two broad categories of traumatic and non-traumatic surgical emergencies the book systematically covers: Techniques of evaluating the patient and applying diagnostic criteria . . . Radiologic procedures that are necessary . . . Anesthesia considerations . . . Fluid and electrolyte replacement.

The patient evaluating techniques, diagnostic steps and surgical treatment are presented step-by-step with each individual entry numbered for simplicity.

Subject matter includes emergencies occurring in the areas of general, orthopaedic, neurologic, ophthalmic, thoracic, plastic, urologic, head and neck, and pediatric surgery.

All who are involved in surgical emergency treatment will appreciate this easy-to-use, time-saving manual.

664 Pages • 50 Illustrations • 1974
Flexible Binding • \$23.75

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Balanced high potency
vitamin B-complex and
500 mg vitamin C

Virtually no odor or
aftertaste

Low priced Rx formula

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#100
Sig: 1 Tab
B.I.D.

Please see complete product information, a summary of which follows:

Each Berocca Tablet contains:
Thiamine mononitrate (Vitamin B₁) 15 mg
Riboflavin (Vitamin B₂) 15 mg
Pyridoxine HCl (Vitamin B₆) 5 mg
Niacinamide 100 mg
Calcium pantothenate 20 mg
Cyanocobalamin (Vitamin B₁₂) 5 mcg
Folic acid 0.5 mg
Ascorbic acid (Vitamin C) 500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B₁₂.

Dosage: 1 or 2 tablets daily, as indicated by clinical need.

Available: In bottles of 100 and 500.

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

ROCHE

The silent disorder: Vitamin deficiency in the postoperative patient

Silent—but
often present in
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Following major surgery,
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As soon as your patients can take oral medication,
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B-complex and 500 mg vitamin C that they need
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Berocca Tablets are not intended for treatment of
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To overcome the B and C deficit
BEROCCA® IS THERAPY
TABLETS Balanced high potency vitamin B-complex and **500 mg vitamin C.**
Virtually no odor or aftertaste. Low priced Rx formula.

Please see facing page for summary of product information.

**The end of surgery
is only the beginning...**



when serious infections* complicate recovery

*due to susceptible organisms

'ANCEF' Is 90% Effective in Serious Bone and Joint Infections

In clinical studies of 30 patients with such infections as septic arthritis and osteomyelitis due to susceptible strains of *Staphylococcus aureus*, 'Ancef' produced good or excellent responses in 90% of the cases.

'ANCEF' Penetrates Bone and Synovial Fluid

Tissue/Fluid	Tissue/Fluid Level (mcg/ml) (Sampling time)	Serum Level (mcg/ml) (Sampling time)
Osteomyelitic Bone	49.4 (1 hour)	30.2 (1 hour)
Osteomyelitic Bone	35.6 (5 hours)	26.0 (5 hours)
Osteomyelitic Bone	10.2 (8 hours)	4.8 (8 hours)
Synovial Fluid	50 (1 hour)	85 (1 hour)
	65 (1-1/2 hrs)	78 (1-1/2 hrs)
	59 (2 hours)	53 (2 hours)
	45 (3 hours)	43 (3 hours)
	37 (5 hours)	32 (5 hours)

(Data from individual patients. All patients received 1 gram IM.)

'ANCEF' Offers the Convenience of Both IV and IM Administration

Adverse Reactions

Adverse reactions reported with 'Ancef' include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment. For a complete list of adverse reactions with 'Ancef' therapy, please see next page.

Warning

In penicillin-allergic patients, cephalosporins should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Please see the next page for a brief summary of the prescribing information.

ANCEF[®]
brand of
CEFAZOLIN SODIUM

Injection: 250 mg, 500 mg and 1 gram vials

meets the challenge, IV or IM

ANCEF[®]

brand of

CEFAZOLIN SODIUM

meets the challenge, IV or IM

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

DESCRIPTION

Ancef[®] (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-[[[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio] methyl]-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

<i>Streptococcus pneumoniae</i> (formerly <i>D. pneumoniae</i>)	<i>Klebsiella</i> species
<i>Escherichia coli</i>	<i>Enterobacter aerogenes</i>
<i>Proteus mirabilis</i>	<i>Hemophilus influenzae</i>

Most strains of *Enterobacter cloacae* and indole positive *Proteus* (*P. vulgaris*, *P. morgani*, *P. rettgeri*) are resistant. Methicillin-resistant staphylococci, *Serratia*, *Pseudomonas*, *Mima*, *Herellea* species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis*, *Escherichia coli*, and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'Ancef' is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen,

intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in premature and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest[®] tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocytopenia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible gram+ cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef[®] (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories

Division of SmithKline Corporation, Philadelphia, PA 19101

A dark, out-of-focus background showing various medical instruments, including syringes and needles, arranged on a surface.

Injectable
Talwin[®]
Brand of
pentazocine
ampuls of (as lactate)
30 mg. 45 mg. 60 mg.

Winthrop



**The
alternative
to opiates.**

See important product information concerning adverse reactions, patient selection, and prescribing and precautionary recommendations on reverse side.

Talwin®
Brand of pentazocine (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence.* Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided. In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it

should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: Certain Respiratory Conditions. The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. As with all strong analgesics, Talwin should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine, as lactate. Constant rotation of injection sites is, therefore, recommended. In addition, animal studies have suggested that Talwin may be tolerated less well subcutaneously than intramuscularly.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions. Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including angioedema, edema of the face, vascular purpura, toxic epidermal necrolysis.

See *Acute CNS Manifestations and Drug Dependence* under **WARNINGS**.

Dosage and Administration: Adults, Excluding Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. When frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: Manifestations. Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are not effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: Uni-Amp®—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.) in boxes of 25.

Ampuls of 1 ml. (30 mg.) in (nested) boxes of 25.
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Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.
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The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

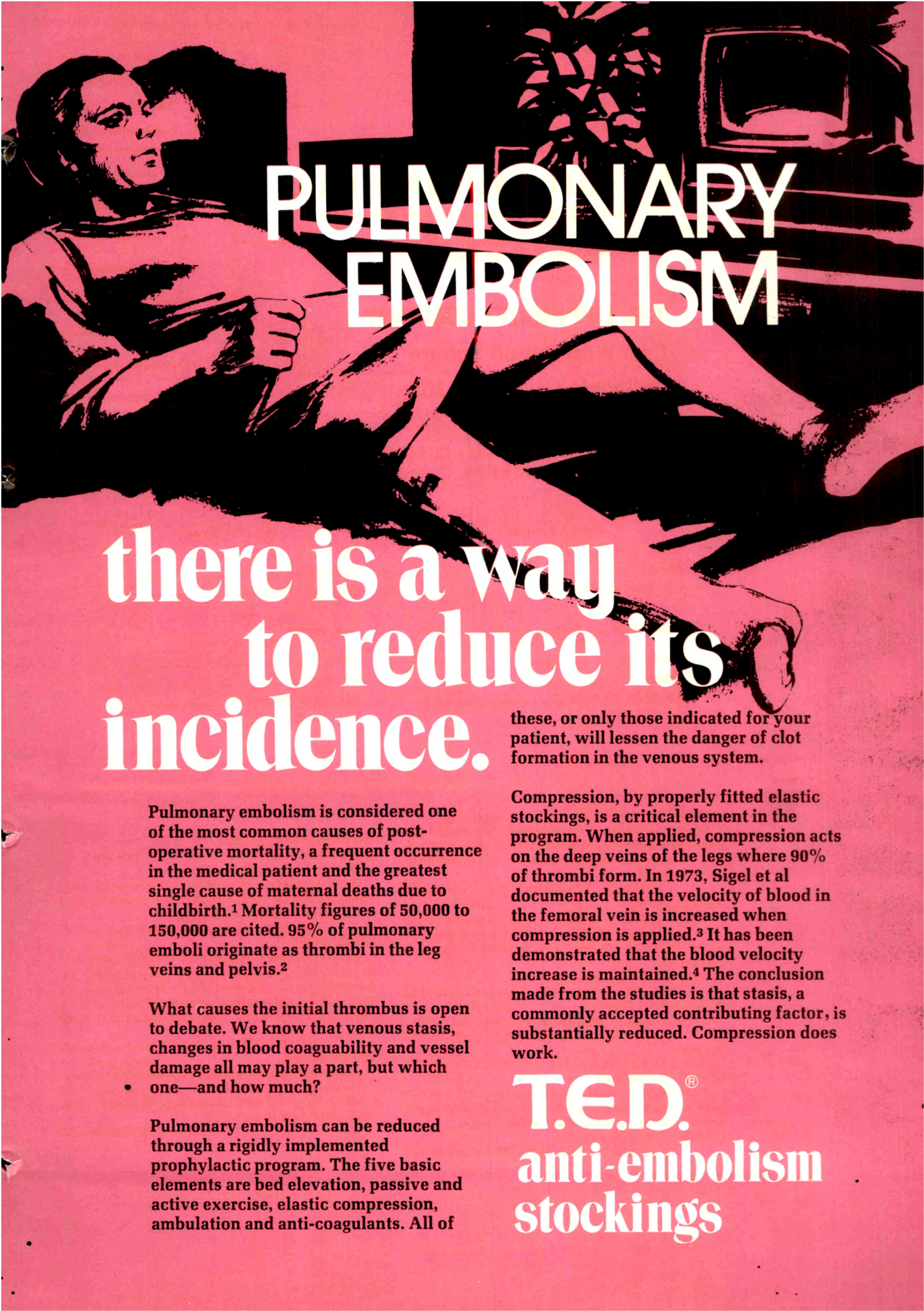
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A black and white photograph of a woman lying in a hospital bed, wearing TED stockings. She is looking towards the camera. The background shows a hospital room with a television and some plants.

PULMONARY EMBOLISM

there is a way
to reduce its
incidence.

Pulmonary embolism is considered one of the most common causes of post-operative mortality, a frequent occurrence in the medical patient and the greatest single cause of maternal deaths due to childbirth.¹ Mortality figures of 50,000 to 150,000 are cited. 95% of pulmonary emboli originate as thrombi in the leg veins and pelvis.²

What causes the initial thrombus is open to debate. We know that venous stasis, changes in blood coagulability and vessel damage all may play a part, but which one—and how much?

Pulmonary embolism can be reduced through a rigidly implemented prophylactic program. The five basic elements are bed elevation, passive and active exercise, elastic compression, ambulation and anti-coagulants. All of

these, or only those indicated for your patient, will lessen the danger of clot formation in the venous system.

Compression, by properly fitted elastic stockings, is a critical element in the program. When applied, compression acts on the deep veins of the legs where 90% of thrombi form. In 1973, Sigel et al documented that the velocity of blood in the femoral vein is increased when compression is applied.³ It has been demonstrated that the blood velocity increase is maintained.⁴ The conclusion made from the studies is that stasis, a commonly accepted contributing factor, is substantially reduced. Compression does work.

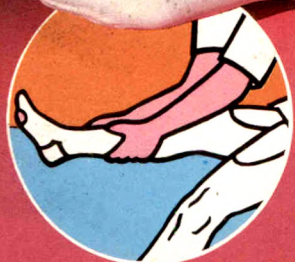
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You can protect your patient from the possibility of pulmonary embolism with the added measure of T.E.D. Anti-Embolism Stockings.

1. Skillman, John J., Postoperative Deep Vein Thrombosis and Pulmonary Embolism: A Selective Review and Personal Viewpoint. Surgery 75:1 Jan. 1974, pp. 114-122.
2. Hume, H., et al, Venous Thrombi and Pulmonary Embolism. Harvard Press: 1970, p. 4.
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Cholangitis With Acute Renal Failure:

Priorities in Therapeutics

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Obstructive cholangitis with acute renal failure is a dramatic syndrome which merits individual definition. Twenty-one patients with acute suppurative cholangitis complicated by rapidly developing renal insufficiency were studied, and the severity of the renal failure, an acute interstitial tubulopathy, bore no significant relationship to the serum bilirubin level. The mechanism of renal damage was clearly related to episodes of septicemia. Increasing experience has modified the approach to treatment. The dominant septic problem can often be controlled by vigorous antibiotic and fluid therapy, allowing time for spontaneous improvement in renal function. All patients thus operated at a distance from the septic episode survived. If emergency operation is required because of persistent or recrudescing sepsis, the necessity for dialysis should be considered first; the circumstances demanding dialysis are defined. The priorities in therapy are then: 1) treatment of the infection, 2) treatment of the renal failure, and finally 3) operation. The moment of the operation depends on the evolution of the sepsis, but should be preceded by dialysis when required.

ORIGINALLY described by Charcot,⁶ a particularly severe form of suppurative cholangitis complicated by acute renal failure has been the subject of numerous studies. Individualized by Caroli⁴ as "uremigenic cholangitis," the association of biliary sepsis with renal failure has too often been considered together with a heterogeneous group of hepato-biliary disorders, pre- and postoperative, called variously "cholemic nephroses" or "liver kidney syndromes."^{16,21}

The lack of clarity in the definition of these syndromes has led to some confusion in treatment. When suppurative cholangitis is associated with renal failure, a variety

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of therapeutic attitudes has been recommended, often based on the conception that the renal failure will remain refractory if the biliary tree is not surgically decompressed as an emergency.^{4,9}

One purpose of this study is to analyze the elements of the association of cholangitis with acute renal failure and their relationship. The second aim is to define the order of therapeutic priorities in this dramatic illness. Particularly, the moment of operation and the place of renal dialysis need to be clarified. Our experience with 21 patients with cholangitis and acute renal insufficiency suggests that certain previous attitudes concerning the syndrome should be reconsidered.

Clinical Material

From 1966 to 1973, in a service specializing in hepato-biliary surgery,[‡] 283 patients were hospitalized with a confirmed diagnosis of cholangitis due to an obstruction of the main bile duct.

In order to study the association of cholangitis with acute renal failure, and to eliminate other conditions that might simulate this syndrome, patients were selected from this group who fulfilled the following criteria: 1) cholangitis, i.e., the association of signs of biliary retention (clinical jaundice, total serum bilirubin more than 3.0 mg/100 ml), and invasive sepsis (temperature of 39° or over and/or chills, plus white-cell count exceeding 10,000/mm³) due to an obstruction of the main bile duct. The nature of the obstacle was verified at operation or autopsy (excepting one patient refusing surgery in whom the obstacle, a stone, was demonstrated on intravenous cholangiogram).

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TABLE 1. Characteristics of 21 Patients with Cholangitis and Acute Renal Failure

Case	Age (yr)	Sex	Nature of Obstacle	Pain	White Cell Count	Blood Culture	Shock	Hepatomegaly	Bilirubin (mg/100ml)	Alkaline Phosphatase	Sepsis duration Before renal Failure (days)	BUN/Creatinine (mg/100ml)	Anuria or Oliguria	Dialysis	From onset of renal failure	Date of Operation (days)	From Admission	Operation	Results
1	75	M	Ampuloma	Rigidity	18,900		+		clinical ++		13	80	+					none	Died on arrival
2	88	F	Stones		22,000	E. coli		+	15.5	9*	1	230	+					none	Died on arrival
3	88	M	Stones	+	40,000				8.3	15*	11	260	+					refused surgery	Recurrent Cholangitis
4	58	M	Ampuloma	+	22,000			+	34.0	38*	50	185		Hemo. postop	2	2		Choledocho-Duodenal Anastomosis	Died
5	63	M	Stones	+	72,300	E. coli	+		17.0	20*	1	180			1	1		T-tube	Died
6	75	F	Cancer Pancreas	+	11,400				36.2	21*	10	270		Perit. postop	4	3		Intra-hepatic Anast.	Died
7	50	M	Ampuloma	+	35,900	Neg.		+	38.0	57*	1	390		Hemo. pre- + postop	2	1		Choledocho-Duodenal Anastomosis	Recovered
8	72	F	Stones		17,900	Neg.	+		14.0	64	4	310	+	Hemo. preop Perit. postop	5	2		T-tube	Recovered
9	59	F	Stones	+	13,900	Moraxella			22.0	23*	10	240			11	5		Hepato-Jejunal Anastomosis	Recovered
10	63	M	Stones		25,700	Proteus	+		6.2	24*	1	240	+		16	14		Choledocho-Duodenal Anastomosis	Recovered
11	73	F	Stones	+	53,700	Klebsiella	+	+	9.5	8.5*	1	120	+		14	8		T-tube	Recovered
12	83	F	Stones		21,600	Neg.			9.3	25*	8	240	+		36	34		Choledocho-Duodenal Anastomosis	Recovered
13	82	M	Ampuloma	+	58,000	Neg.	+	+	8.6	20*	2	90	+		15	13		Choledocho-Duodenal Anastomosis	Recovered

TABLE 1. (continued.)

14	60, F	Neo-plasia	+	23,300	E. coli	+	+	+	18	420*	4	320	+	17	12	Cholecho- Duodenal Anastomosis	Recovered
15	70, M	Stones	+	18,500	Pyocya- neus	+	+	+	28.0	224	2	158		9	6	Cholecho- Duodenal Anastomosis	Recovered
16	79, M	Stones	+	12,300					9.9	132	1-3	148/4.8		21	11	T-tube	Recovered
17	70, F	Stones	+	18,400	E. coli	+	+	+	1.6	80	1-3	155/9.5		8	5	T-tube	Recovered
18	70, M	Cancer Pancreas	+	20,000	Neg.	+	+	+	41.0	45*		210	+	13	13	Cholecho- Duodenal Anastomosis	Recovered
19	81, F	Stones	+	24,000	E. coli	+	+	+	52.0	499	9	160		6	6	T-tube	Died Hemorrhage
20	83, F	Cancer Gall- bladder	+	11,800	Neg.				3.5	52	21	180	+	7	6	Hepatic. Enteric Anastomosis	Died Myocard. Infarc.
21	78, F	Stones	+	19,800	E. coli	+	+	+	15.0	200	1-3	160	+	10	1	Cholecho- Duodenal Anastomosis	Died Coma

*Bodansky units (normal up to 8 units), otherwise international units (normal up to 45 units)

2) acute renal insufficiency, defined as an elevation of BUN over 40 mg/100 ml or serum creatinine exceeding 2.0 mg/100 ml with a ratio of concentration of urine urea to blood urea (U/P urea) of less than 8, corresponding to the usual definition of renal failure.¹⁰

Several patients meeting these criteria were eliminated, because they presented another element capable, by itself, of influencing renal function. Thus, patients with acute pancreatitis, intra-abdominal abscess, bile peritonitis, or cirrhosis were excluded. No postoperative patients were included. Renal failure occurring only postoperatively, even if authentic cholangitis existed preoperatively, was not considered a part of the pure syndrome of uremigenic cholangitis.

Twenty-one of the 283 patients were found to meet these requirements and were retained for study. Table 1 presents the clinical data concerning the 10 male and 11 female patients. The average age was 72 years.

Analysis of the Three Elements of the Syndrome

Sepsis

The signs of infection were severe, with chills and fever exceeding 39° and marked leukocytosis occurring in all patients; septicemia and shock were documented together in 9 patients. Obtundation or coma was observed in 15 patients. Bile culture was positive in 12 patients and described as purulent in others at operation. The culture techniques may have been deficient in view of the reported incidence of near 90% positive bile cultures in the presence of common duct stones, and the rising incidence of recovery of anaerobic organisms with newer technological advances, as emphasized recently by Gorbach and Bartlett.¹³

Biliary Obstruction

The obstruction of the common duct was of two principal etiologies: lithiasis (13 patients), and tumor of the ampulla of Vater (4 patients). Other tumors about the lower common duct accounted for the remainder. Symptoms and signs related to the biliary tree were constant and generally severe. The average bilirubin was 20.0 mg/100 ml and in 5 patients was over 30 mg/100 ml. Similarly, the serum alkaline phosphatase was elevated but in a capricious fashion in relation to the bilirubin, and in 5 cases was only mildly increased. Almost all patients had pain and tenderness in the right upper quadrant; 4 had rigidity. The liver was palpably enlarged in just less than half the patients. Previous attacks related to the biliary tree were elicited in 12 of the 13 patients with lithiasis, often dating back several years. In 5 patients the major febrile episode leading to the renal failure was heralded by one or more lesser attacks of right upper quadrant pain and fever in the month preceding.

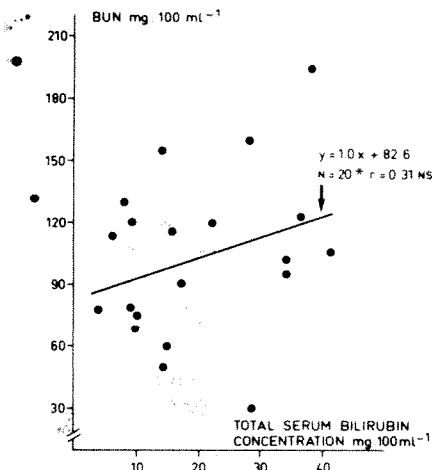


FIG. 1. Relationship between BUN and total serum bilirubin concentration. (In one patient simultaneous values were not available)

Renal Insufficiency

Twenty patients gave no previous history of renal disease. In one patient there was previous mild chronic impairment of renal function which was aggravated by the cholangitis, with renal function diminishing by more than half, then returning to the previous baseline.

Anuria or oliguria was recorded in 12 patients (urine output less than 500 ml per 24 hours). Nine patients had high output renal failure, characterized by a urine urea to plasma urea ratio (U/P) of less than 8, associated with a high urinary sodium. The renal problem appeared promptly (within 48 hours) after the onset of pain and fever in eleven patients; in the remainder it was documented later, generally during the second week of illness. The onset of renal failure coincided with chills or elevation of temperature above 39° in all patients except one, and coincided with shock in 9. No patient had undergone operation before the onset of renal failure.

The severity and duration of the renal disorder was quite variable. Patients have been arbitrarily classified into 3 groups of mild, moderate, and severe renal failure, defined according to the following criteria: 1) oliguria or anuria (urine volume less than 500 ml per 24 hours); 2) necessity for dialysis; 3) BUN of 100 mg/100 ml or greater; 4) plasma potassium of 5.0 mEq/litre or over; 5) plasma bicarbonate of 20 mEq/litre or less. Patients exhibiting one or none of these 5 features were classified as having mild renal failure; with more than one but less than four, moderate; and with 4 or 5 of the criteria, as severe. Only 17 patients could be classified because data was not complete for 4 patients seen early in the series. Thus defined, 6 patients had mild renal failure, 2 severe, and the remainder moderate.

Six patients underwent preoperative dialysis; 3 peritoneally and 3 by hemodialysis. Four of these patients required dialysis both pre- and postoperatively. Two patients were dialyzed in the postoperative period only. In survivors the renal function eventually returned to pre-illness levels.

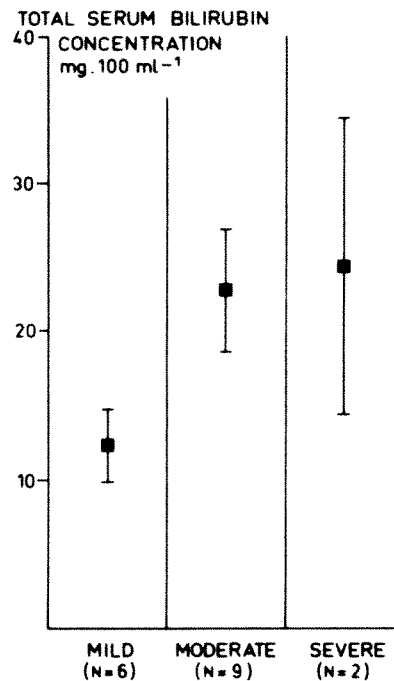


FIG. 2. Relationship between total serum bilirubin and renal status of patients classified into three groups by severity of acute renal failure (see text). Means $\pm$ standard error of the means (SEM) are represented. Differences between the three groups were not significant, as assessed by Student's *t*-test. Only 17 patients are included since simultaneous data sufficient to classify 4 patients seen early in the series were not available.

The renal failure was considered organic in all cases, and the mechanism appeared related temporally to an episode of septicemia, which was documented in 10 patients.

The relationship of the serum bilirubin concentration to BUN and to the severity of renal failure is expressed in Figures 1 and 2. While there was a tendency for higher levels of bilirubin to be associated with more severe renal involvement, the correlation is not statistically significant.

Results of Treatment

Two patients died in shock within a few hours of their arrival. One patient refused operation. This left 18 patients for evaluation of therapy. All patients were given vigorous fluid replacement, including blood and plasma as needed, and furosemide if urine output was low. All patients were given antibiotics. All of the 18 patients underwent surgical exploration. The outcomes of therapy are presented in Table 2.

The first 3 patients, treated early in our experience, were managed following the then-current doctrine of emergency operation. In one of these patients, the course after rehydration and antibiotics was followed for several hours; as soon as temperature and urinary output returned to normal, operation was performed. All 3 of these patients died.

The 15 subsequent patients were observed longer under the influence of fluid and antibiotic therapy. Four outcomes were seen. In two patients the infection persisted (cases 7 and 8). Both underwent emergency hemodialysis, then were operated on and both survived.

The second course was seen in two patients (cases 9

TABLE 2. Outcome of Treatment in 18 Operated Patients.

Therapeutic Attitude	No. of Patients	Survivors	Deaths
Emergency Operation: (cases 4-6)	3		3
Delayed Operation:			
1. Sepsis Continues: Emergency Dialysis Then Operation (cases 7-8)	2	2	
2. Improvement, Then Relapse: Urgent Operation (cases 9-10)	2	2	
3. Improvement: Operation After Renal Recovery (cases 11-17)	7	7	
4. Improvement, But Other Major Organ Failure (cases 18-21)	4	1	3

and 10) who showed initial improvement which lasted several days. In one, the jaundice persisted, but her renal function returned almost to normal (BUN 40 mg/100 ml). A relapse of sepsis at this point led to emergency operation and recovery. In the other patient the BUN had fallen markedly to 50 mg/100 ml over a 16 day period. At this point the fever returned and he was operated on as an emergency and recovered.

The third outcome was that of sustained improvement in terms of the infection. In 7 patients fever and elevated white-cell count fell rapidly and did not return, allowing time for spontaneous improvement in renal function. All these patients did show progressive improvement in renal function. This permitted elective operation at an interval of from 8 to 36 days (median 15) following the onset of renal failure, and from 5 to 34 days (median 11) following admission to our unit. All 7 patients in this group survived. The BUN in these cases averaged 176 mg/100 ml initially and had returned to an average of 35 mg/100 ml at the time of operation. Antibiotics were continued in most, but in some were stopped after 10 days. In none did signs of sepsis recur. In 4 the signs of biliary obstruction improved concomitant with improvement in renal function. In 3, the BUN returned towards normal despite persistence of elevated bilirubin and alkaline phosphatase. At operation the procedure consisted of a bilio-enteric anastomosis in the one case of tumoral obstruction, and in cases of lithiasis, was cholecystectomy, removal of stones and drainage via T-tube in 3 and choledocho-duodenal anastomosis in 3.

The fourth and final evolution observed under antibiotics includes 4 patients who showed improvement with

antibiotics but in whom other major organ failure supervened (i.e. cardiac, neurologic).

In one of these 4 (case 18) gastrointestinal hemorrhage developed requiring emergency operation after dialysis; this patient survived. Another (case 21) was operated for recrudescence of sepsis in coma after several cardiac arrests and eventually died of cardiac causes. The remaining two died postoperatively, one from cardiac failure, and one, in whom choledochooduodenostomy was performed, from diffuse hemorrhage associated with a blood clot blocking the anastomosis. The occurrence of other major organ failure in these patients, even though they were improving in terms of their sepsis, created a disparate group in whom the choice and timing of operative biliary drainage was difficult.

Discussion

The selection of patients for this study may seem unnecessarily restrictive. Patients with sepsis and jaundice in whom a biliary obstacle was not proven have been eliminated because the absence of demonstrable biliary obstruction raises a question as to the validity of the diagnosis. Other lesions, *e.g.*, the jaundice of septicemia or leptospirosis, can cause a confusingly similar picture. This requirement almost surely excluded patients with true cholangitis but in whom the obstacle, *e.g.*, a stone, had passed spontaneously. Only when it is certain that one is dealing with a single clinical entity can appropriate conclusions be drawn regarding its evolution and treatment. Likewise, the presence of any factor that might, alone, be related to renal insufficiency, such as acute pancreatitis or sepsis outside the biliary tract, caused elimination of the patient because the relationship of biliary retention to the renal failure is then obscured. Since the postoperative state introduces a variety of factors which can influence renal function, only patients with preoperative renal failure were included.

The presence of cirrhosis, even the secondary biliary type, similarly would not allow evaluation of the pure syndrome.

The etiology of cholangitis with renal failure is primarily lithiasis, followed by ampulloma, as noted by Caroli.⁴ These causes of biliary obstruction, frequently partial or intermittent, are most often complicated by sepsis, in contradistinction to tumors of the pancreas and bile duct which rarely become infected, as noted by Sherlock and others.^{5,20} In this series, ampullomas occurred in younger males, without previous biliary disease, in contrast to the typical picture of lithiasis, occurring predominantly in elderly females with months, sometimes years, of prior biliary troubles.

Renal failure is occasionally associated with many diseases that produce jaundice. Although the term "hepato-renal syndrome" was originally coined by Merklen in 1915¹⁷ in considering a case of cholangitis with

renal failure, a multitude of conditions has been included under this rubric, and a clearer definition was needed. Recently Conn⁷ has argued for restriction of the term "hepato-renal syndrome" to a type of renal failure occurring in association with cirrhosis, a clarification which we heartily support.

During the obstructive jaundice, the responsibility of the liver for the production or non-detoxification of substances noxious to the kidney is controversial. It is most likely that the renal lesion associated with jaundice in cholangitis is related to infection, septicemia, and reduced effective renal perfusion.¹⁵ As such, it is not different from the acute interstitial nephropathy seen in a variety of conditions affecting renal hemodynamics which it closely resembles clinically, biochemically, and histologically.^{8,11}

In our patients the onset of renal insufficiency coincided in every case with an infectious state including shaking chills, and the clinical and laboratory findings were the same as those described in the tubulopathy occurring in septic settings without hepato-biliary disease.^{14,18} There was no significant correlation between degree of bilirubinemia and the gravity of the renal failure, and in several cases the renal lesion improved spontaneously with clearing of infection but without change in the bilirubin level.

The responsibility of biliary retention, particularly of conjugated bilirubin, in the production of renal failure has been suggested.^{1,2,9,22} It appears likely that excess conjugated bilirubin renders the kidney more susceptible to ischemic insult.⁹ However, in the absence of infection, such acute renal failure does not occur, even in extreme degrees of biliary retention, e.g., neoplastic obstruction.³ Renal failure in these jaundiced patients with suppurative cholangitis remains a rare event and this study does not confirm or deny that icteric patients are any more likely to develop a renal lesion than others with sepsis. It appears that renal function can improve independent of the serum bilirubin level.

The renal lesion occurring in obstructive cholangitis should not be included under the term "hepato-renal failure," nor should it be considered a special or mystical form of kidney injury by an ailing liver. It is best considered and treated as an acute interstitial nephropathy caused by infection-altered renal hemodynamics.

In the treatment of the three components of the syndrome of acute obstructive cholangitis with renal failure, the infectious element is predominant. In contrast to the experience of Glenn and Moody, Reynolds and Dargan, and others,^{12,19,20} our experience shows that the sepsis is not routinely refractory to antibiotic therapy.

Either signs of sepsis regress, or infection persists or worsens. In the latter case emergency operation is indicated. When sepsis continues, the renal and metabolic status is evaluated, and if renal failure is moderate or

severe, hemodialysis should be undertaken before operation. We have selected as indications for dialysis a serum potassium of 5.5 mEq/l or greater, BUN over 100 mg/100 ml or acidosis with a serum bicarbonate less than 15 mEq/l. Some patients exhibit an extremely rapid rate of change in these metabolic measurements and this should be taken into account, sometimes dialyzing for a less severe but rapidly changing disturbance. Following such a program, no patients have been lost due to complications of the renal failure.

In those patients who initially improve, three courses were observed: 1) a recrudescence of the signs of sepsis. At the first sign of returning sepsis, these patients are managed as are patients with persistent sepsis, i.e., dialysis if necessary; urgent operation. 2) Continued improvement of sepsis with existence of other major organ failure (pulmonary, cardiac, hemorrhage). The indication for operation remains but the risk is greatly increased. Judgment of the moment to operate is delicate, weighing the probable evolution of the other problems against the likelihood of recurrent sepsis. No guidelines concerning these patients can be proposed. 3) Continued improvement of sepsis. The number of patients who maintained improvement is striking. This may be related to spontaneous improvement in the degree of biliary obstruction in some patients, but this does not seem to be a prerequisite. That germs are not eliminated from the bile duct by antibiotics is demonstrated by the high number of positive bile duct cultures; one patient, after extensive antibiotherapy and regression of jaundice, still harbored 4 different organisms in his biliary tract. What deserves emphasis is the fact that sepsis can often be controlled allowing time for 1) the renal disorder to resolve spontaneously, and 2) the operation, always indicated, to take place electively under ideal conditions with resultant improvement in mortality (7 survivors of 7). It thus seems to be most desirable to abstain from operation for as long as necessary to allow renal status to return to normal. Operating immediately, or when temperature, hemodynamic status, and diuresis first become normal, has not provided encouraging results.

An additional reason for awaiting the maximum patient improvement depends on the fact that in patients with choledocholithiasis, cholangitis, and acute renal failure the obstruction is most often complete, the stones frequently multiple. The stones, if multiple, may involve the intrahepatic ducts, or a clay-like mold of the bile duct may form (observed in two of our patients). In such patients, the simple placement of a T-tube is evidently insufficient. The extensive procedure of complete opening of the ducts, preferably with cholangiographic control, and frequently with bilioenteric anastomosis, is most often required, and for this the patient must be in optimal condition.

Stated otherwise, the moment of surgical intervention

is determined by the evolution of the sepsis. An operation will always be required, but its timing should be in relation, first, to the infection, and second, to the renal insufficiency. The biliary obstruction passes to a secondary role, and the renal insufficiency is treated on its own independent merits and/or in relation to an emergency operation when required. The order of priorities is thus: 1) treatment of the infection; 2) treatment of the renal failure; and last of all, 3) operation. The gravity of the infection modifies the timing, but not the chronology of the different steps.

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Bilateral Carotid Aneurysms Secondary to Radiation Therapy

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A patient was seen with symptomatic, rapidly expanding aneurysms that developed in both carotid arteries 4 years after bilateral radiation to the neck, left combined mandibular resection, and radical neck dissection. The presenting symptoms were pain and transient ischemic attacks of cerebrovascular insufficiency. The aneurysms were treated uneventfully by resection and vein-graft replacement at 15-day intervals. Microscopy demonstrated typical radiation changes. Effects of radiation on arteries are reviewed.

RADIATION is known to produce changes in the small vessels.²⁰ Few reports have appeared in the literature describing its effect on larger vessels.^{6,9,13,14,18} Arteriosclerosis may be induced prematurely, and the irradiated vessels have been known to rupture. Aneurysm formation secondary to radiation has not been reported, to the best of our knowledge.

Aneurysms of the carotid artery are relatively rare. The earliest report of bilateral aneurysms of carotid arteries appeared in 1971.³ Subsequently, a series of 5 patients with bilateral aneurysms was reported.¹⁰ Various etiological factors responsible for aneurysm formation

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have been described, but previously the list has not included radiation changes.

This paper describes a patient with bilateral true carotid artery aneurysms that developed 4 years after treatment of carcinoma of the left tonsillar fossa by radiotherapy and radical surgery. The aneurysms were treated by resection and vein-graft replacement, performed 15 days apart without morbidity. Microscopic sections showed typical radiation changes but no arteriosclerosis.

Case Report

A 56-year-old man initially was admitted to Metropolitan Hospital Center in January, 1969, for diagnosis and treatment of a mass in the left tonsil. Biopsy confirmed the diagnosis of infiltrating squamous-cell carcinoma. He was treated with radiotherapy consisting of 3,000 rads bilaterally, delivered from a midline port over a 4-week period. Five weeks later, combined mandibular resection in continuity with primary site was performed on the left side. Examinations of the patient at regular intervals

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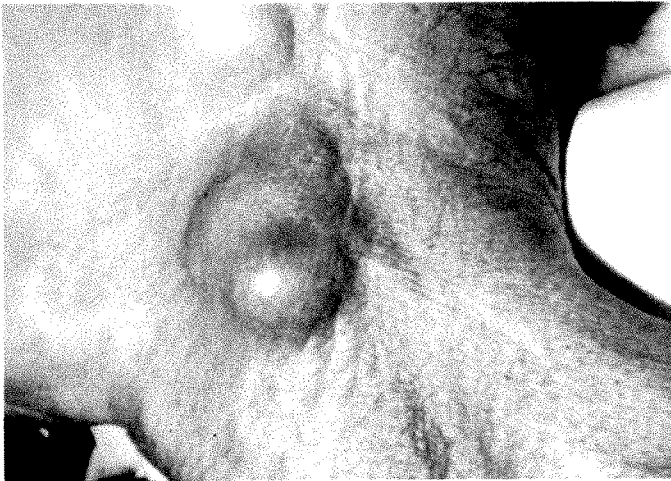


FIG. 1. An expanding pulsatile mass on the left side of the neck developed 4 years after bilateral radiotherapy and left radical neck dissection with mandibular resection. A similar mass appeared on the right side during preoperative evaluation.

showed no evidence of recurrence. In May of 1974 he was readmitted because of a pulsatile mass on the left side of the neck (Fig. 1). During 15 days of evaluation, the aneurysm enlarged and became painful, and a similar mass evolved on the right side. Bruits were audible bilaterally. All peripheral pulses were palpable. There were no foci of infection. Blood pressure was 130/80. ECG showed no abnormality, and serum lipids were within normal limits. The clinical diagnosis was bilateral carotid artery aneurysms secondary to operative trauma on the left and arteriosclerosis on the right.

Spontaneously on the sixth hospital day, transient right hemiparesis developed, but disappeared within 24 hours. Subsequently, percutaneous transfemoral carotid angiography, including the intracranial circulation, demonstrated aneurysms 4 cm in diameter, but no other vascular pathology (Fig. 2A). Compression of the left common carotid artery during contralateral selective injection showed good cross-filling from the right side (Fig. 2B).

On 5/29/74, under general anesthesia, exploration of the left side of the neck disclosed a fusiform aneurysm 4 cm in diameter involving common carotid and proximal internal carotid arteries. The external carotid artery was fibrotic and occluded. Adjunctive measures (high FiO_2 , hypercarbia, and venous hypertension induced with rapid infusion of low-molecular-weight dextran) were used to prevent cerebral ischemia during cross-clamping. Internal carotid artery stump pressure was 90 mm Hg, so that internal shunt was not used. After adequate heparinization and cross-clamping, the aneurysm was resected, and the arterial flow was reestablished using a reversed saphenous vein graft placed end-to-end. The occlusion time was 30 minutes, and no neurological deficit was found postoperatively. On 6/14/74, the second aneurysm was resected, and continuity was restored with a vein

FIG. 2A. Preoperative percutaneous transfemoral carotid angiography demonstrated both aneurysms (arrows) arising at the level of the carotid bifurcations.



graft. The external carotid artery on the right side appeared normal, and it was reimplanted end-to-side into the vein graft. Occlusion time was 40 minutes, and again the patient recovered without neurological deficit.

The resected aneurysms were studied microscopically

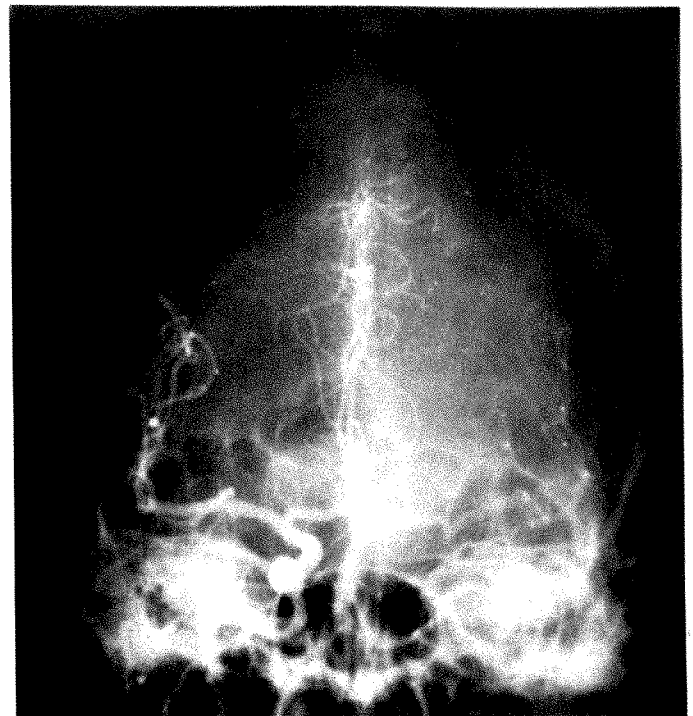


FIG. 2B. Compression of the left common carotid artery at the time of selective right carotid injection with opacification of anterior and middle cerebral arteries demonstrates cross-filling, indicating the probability of safety of cross-clamping on the left side. (Left internal carotid stump pressure was 90 mm Hg, mean, interpreted as precluding the necessity of internal shunt during resection and vein-graft replacement.)

using hematoxylin and eosin, Verhoff stain for elastic fibers, and phosphotungstic acid hematoxylin stain for fibrin. Hyperplasia, edema, fibrosis, and fibrinoid degeneration of intima were evident (Fig. 3A). Large, foamy histiocytes were found scattered in subintima, forming foam-cell plaques (Fig. 3B). Thickening, collagenization, irregular fragmentation, and marked disruption of the elastic fibers were present in the media (Fig. 3C). Destruction of the internal elastic lamina was evident (Fig. 3C). The adventitia was thickened from newly formed collagen. No microscopic evidence of atherosclerosis was seen.

Postoperative angiography showed patent grafts and right external carotid artery. The patient remains asymptomatic, and his course is being followed regularly in the outpatient clinics.

Discussion

Carotid artery aneurysms form less than 1% of all peripheral aneurysms.^{5,10} Hardin reviewed 56 cases from the previous literature and added eight cases.⁷ Congenital carotid aneurysms are rare. Bilateral carotid aneurysms are seen even less frequently, and only 6 cases have been reported.¹⁰ Most carotid aneurysms are fusiform; the saccular form is unusual. The most common causes are atherosclerosis and trauma.⁵ Less frequent causes are infection (syphilis, tuberculosis), Marfan's syndrome, and cystic medial necrosis.^{5,15,16} Aneurysms after angiography¹ and carotid artery reconstruction² have been reported recently. The case presented here illustrates an additional etiological factor—radiation.

Effects of radiation on large vessels have been studied both experimentally and clinically. Lindsay demonstrated intimal thickening and alteration of the internal elastic lamina with hyaline swelling, beading, and fragmentation in aortas of dogs.¹²

The foam-cell plaques within subintima are characteristic of radiation injury. They have been demonstrated in acute as well as chronic preparations in both small and large vessels.¹⁷

Segmental aortic disease with intimal and adventitial thickening has been reported 2½ years after irradiation to the chest.¹⁸ Premature arterial occlusive disease in children after irradiation for sympathicoblastoma of the adrenal gland has been shown.⁶ A series of 11 cases of blood-vessel rupture secondary to radiation changes has been published.¹³ Fragmentation of the elastic tissue has been described in microscopic and ultramicroscopic sections in a previous case report from this department of pathology.¹⁴ Although rare, aneurysm formation seems to be a logical end-result of weakened and partially disrupted arterial wall.

Carotid aneurysms usually present as asymptomatic or painful pulsatile cervical masses associated with systolic

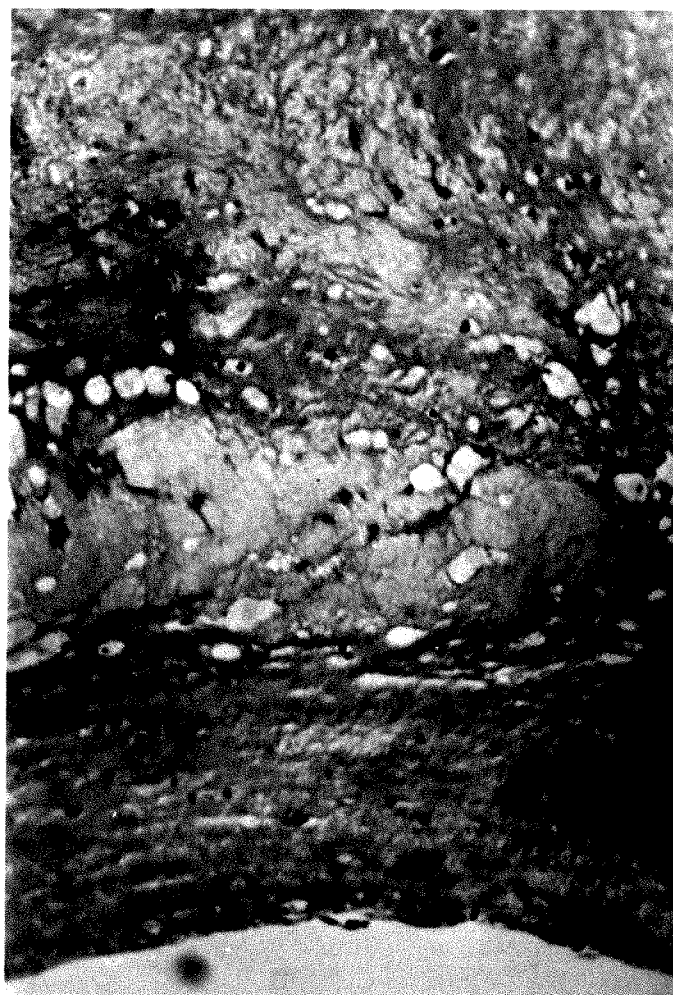


FIG. 3A. Microscopic study of the resected specimens showed hyperplasia, edema, fibrinoid degeneration, and duplication of the intima.

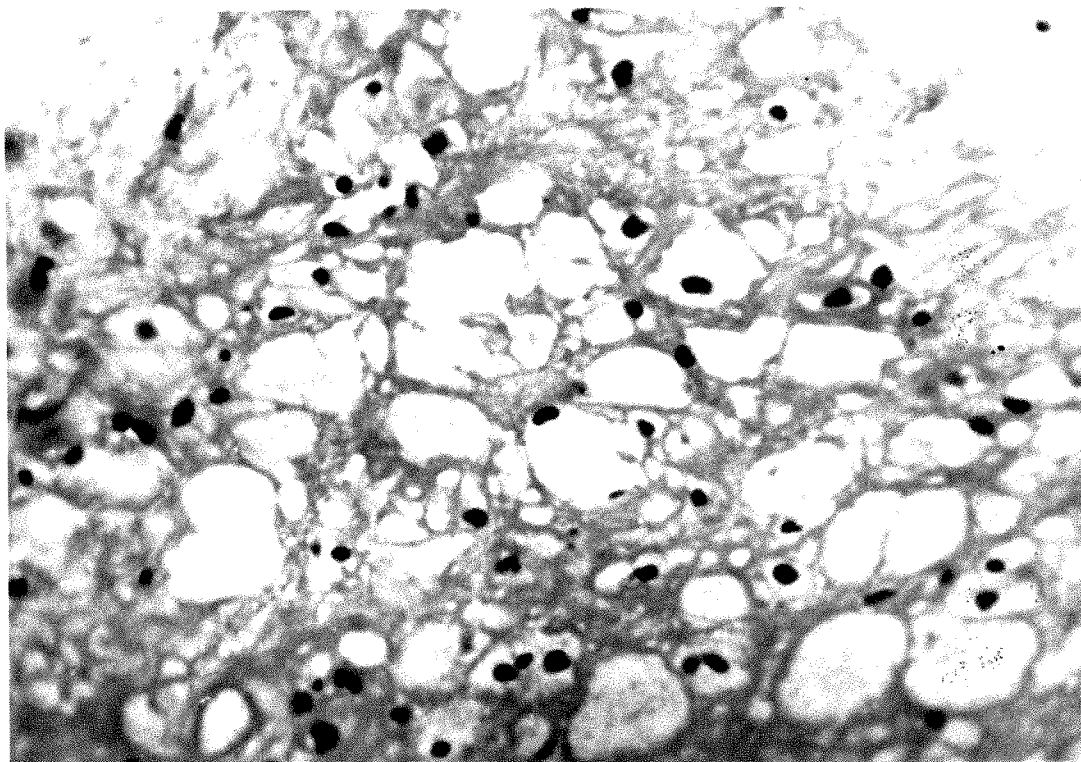
bruits. Transient ischemic attacks secondary to embolic phenomena from turbulent flow have been reported.¹⁰ Unusual presentations are dysphagia, respiratory obstruction, and oropharyngeal rupture.¹⁵

The presently accepted surgical management of aneurysm of a carotid artery is resection and end-to-end anastomosis or graft replacement,^{5,10} first reported in 1955. Ligation should be reserved for unusual circumstances, e.g., technical unfeasibility, infection.

Maintenance of adequate cerebral perfusion during clamping of extracranial vessels is a prime concern of vascular surgeons. Appropriate preoperative angiographic evaluation to demonstrate or rule out associated occlusive lesions and cross-filling is helpful in selecting a safe technique.

Resections of carotid aneurysms without regard to measures for cerebral protection incurred neurologic complications in 29% of cases. Despite the use of some form of protection, neurologic deficits still developed in

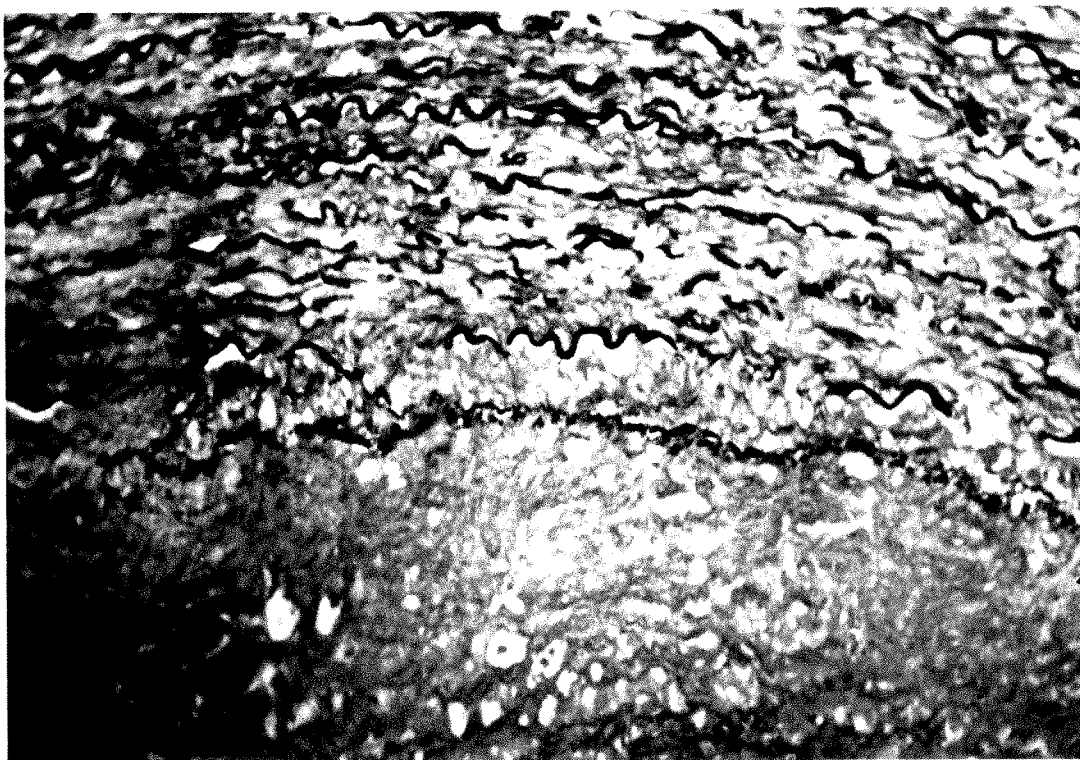
FIG. 3B. Large, foamy histiocytes were found in the subintima, forming foam-cell plaques.



19% of cases.¹⁵ In two cases, neurologic complications were attributed to the use of internal shunts.¹⁰ It is believed these inordinately high complication rates represent occurrences during the historic development of surgery of the carotid artery.

No technical difficulties with dissection or bleeding were encountered in our operative experience, nor in those reported, despite previous local intense irradiation. No clinical or angiographic evidences of abnormality of healing of skin or arteries were observed.

FIG. 3C. Fragmentation and marked disruption of internal elastic lamina are seen.



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An Investigation of Endocardial Viability Ratio in Myocardial Failure Following Prolonged Hemorrhagic Shock

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Previous work has documented prolonged survival in dogs subjected to hemorrhagic shock when intra-aortic balloon counterpulsation (IABC) was instituted in the presence of a 25%-50% reduction in the slope of the left ventricular function curve. Little benefit was noted in the presence of a 75% reduction in slope. In this study, myocardial failure was created in ten dogs by varying periods of hemorrhagic shock. The Endocardial Viability Ratio (EVR) was selected as a method of assessing coronary subendocardial perfusion and was evaluated as a potential method of selecting patients with myocardial failure most likely to benefit from IABC by noting the correlation between EVR and the slope of a simultaneously constructed left ventricular function curve. A significant correlation ($r = .72$, $p < .001$) was noted. The data suggest that a major factor in myocardial failure following hemorrhagic shock is deficient subendocardial coronary perfusion. Variability in data points would make selection of patients on the basis of EVR difficult.

IN recent years the principle of intra-aortic balloon counterpulsation (IABC) has become an increasingly attractive approach to support the failing myocardium.^{2,4,6,7,11} Selection of patients most apt to benefit from IABC is less well established and a clinically applicable method of projecting the survival rate of individual patients is required. We have recently conducted an investigation of the usefulness of IABC in the treatment of myocardial failure associated with hemorrhagic shock. Believing the potential degree of support offered by IABC to be a function of the severity of myocardial failure, we correlated the slope of the ventricular function curve with the improvement in myocardial function associated with the addition of IABC.⁹ The results of that investigation clearly indicated that

optimum benefit from IABC was achieved when the slope of the left ventricular function curve was decreased 25%-50% from baseline, with no significant benefit noted in the presence of a 75% reduction. The present study was undertaken to determine the role of coronary perfusion in the observed benefits of IABC. By using a clinically applicable technique of assessing coronary perfusion, a method for selecting hemorrhagic shock patients for IABC treatment might also be derived.

Methods

Coronary perfusion, or "supply" to the myocardium is in part a function of the relationship between aortic root and ventricular diastolic pressures. The "demand" of the myocardium correlates most closely with the area beneath the ventricular systolic pressure curve.¹⁰ By substituting left atrial diastolic pressure for ventricular diastolic pressure, and aortic systolic pressure for ventricular systolic pressure, Phillips, et al.⁸ have recently expressed this demand: supply ratio mathematically as the Endocardial Viability Ratio (EVR):

$$EVR = \frac{(MDP - MLP) \cdot T_2}{MSP \cdot T_1}$$

where MDP = mean diastolic pressure
MLP = mean left atrial pressure
MSP = mean systolic pressure
 T_1 = systolic interval
 T_2 = diastolic interval

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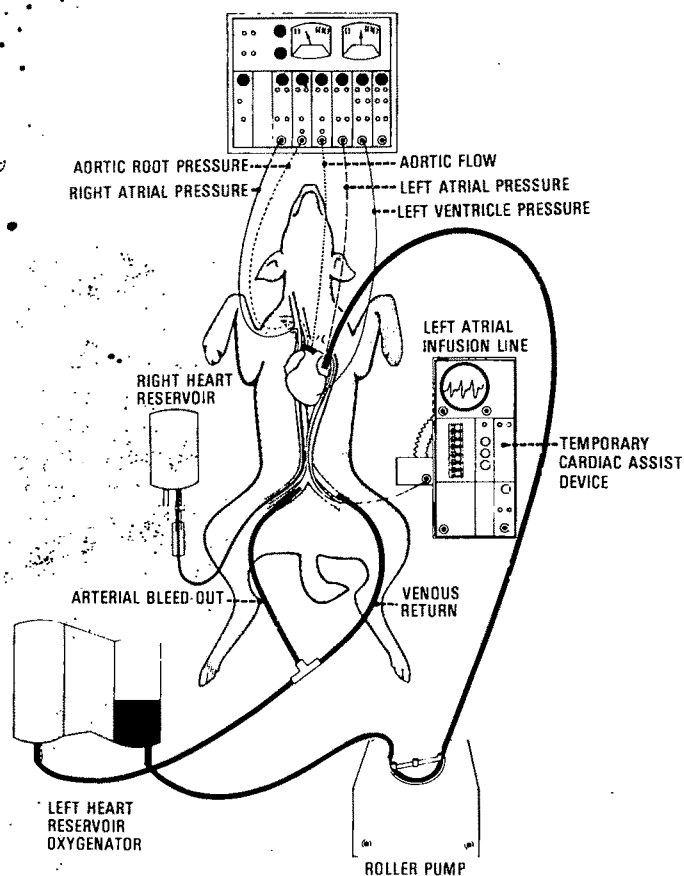


FIG. 1. Technique employed for maintaining shock state and data collection.

Although applied originally in patients with primary cardiogenic shock, the ease of clinical application of this method led us to employ it in our hemorrhagic shock model.

A. Preparation of Animals

After anesthetization with pentobarbital sodium and endotracheal intubation, mongrel dogs were connected to monitoring devices as illustrated in Figure 1. Parameters pertinent to this investigation are: right atrial pressure (RAP), left atrial pressure (LAP), aortic pressure (AP), and aortic flow (AF). The particular details of preparation

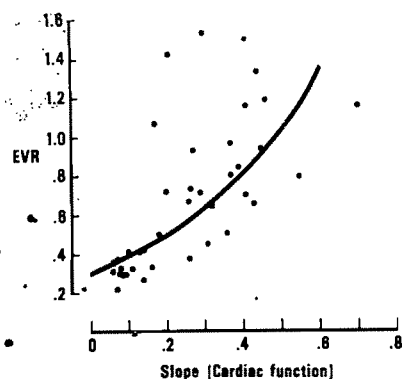


FIG. 2. Graphic relationship between EVR and the slope of left ventricular function curve.

TABLE 1. Reduction in Slope of the Left Ventricular Function Curve

		25%	50%	75%
EVR	$\bar{x}$	.917	.786	.339
	s.e.m.	.072	.110	.018
	n	12	12	14

Mean ($\bar{x}$) and standard error of the mean (s.e.m.) for EVR. Data are arranged as they related to per cent reduction in slope of the left ventricular function curve.

of animals and the creation of degrees of myocardial failure by varied periods of hemorrhagic shock have previously been presented.⁷

B. Data Collection

The slope of the left ventricular function curve was constructed by plotting left atrial pressure and aortic flow* simultaneously on an X-Y recorder† during infusion of 100 ml of an oxygenated mixture of whole blood and balanced salt solution into the left atrium at a rate of 10 ml/sec. During infusion, blood was withdrawn from the venous cannula at a rate sufficient to maintain right atrial pressure constant, thus avoiding changes in right ventricular performance.

Simultaneously, left atrial pressure and aortic pressure signals were recorded on magnetic tape for subsequent calculation of EVR using an IBM 1130 computer. Ten

*Carolina Medical Electronics non-cannulating square wave flow probe.

†Mosely Autograph, Model 2050 AM X-Y Recorder.

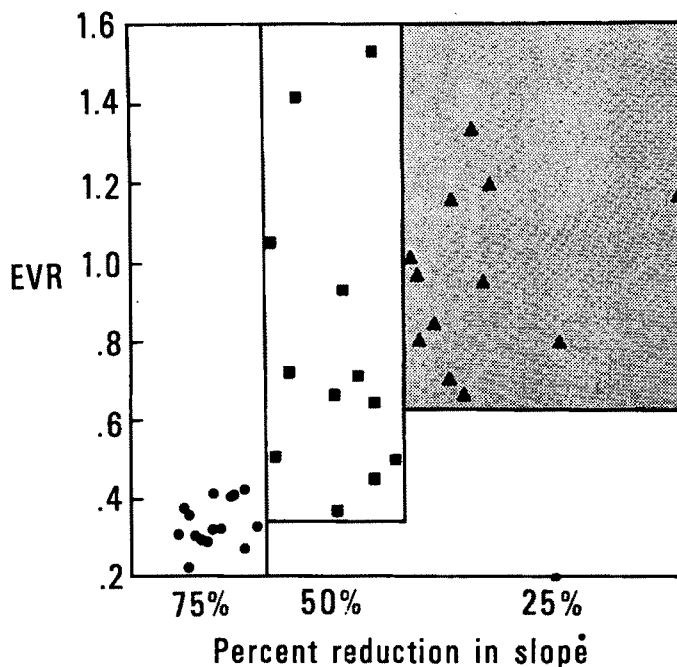


FIG. 3. EVR is superimposed on the ranges of reduced slope of the left ventricular function curve previously associated with significant benefit (25%—50%) and lack of significant benefit (75%) associated with IABC therapy.

dogs were used. After attachment of monitoring devices as described above, a baseline measurement of the slope of the left ventricular function curve and a computation of EVR were obtained. All animals were then bled through an arterial cannula into the oxygenator reservoir until the mean aortic pressure was reduced to 40 mm Hg. This pressure was maintained by either infusion or withdrawal of fluid. At 30 minute intervals, as myocardial function deteriorated, the slope of the left ventricular function curve was measured, expressed as per cent decrease from baseline, and compared to a simultaneous calculation of EVR.

Results

Thirty-eight simultaneous determinations of EVR and the slope of the left ventricular function curve were analyzed.

The mean EVR and standard error are grouped in Table 1 as they relate to percent decrease in the slope of the left ventricular function curve.

The correlation between EVR and slope of the function curve is graphically illustrated in Figure 2. An r value of .72 was obtained ($P < 0.001$).

Superimposed on the data points in Figure 3 are the ranges of reduction in slope of the left ventricular function curve for which we have previously determined either beneficial effects of IABC (25%—50%) or no benefit from IABC (>75%).

Discussion

A mean EVR of .78 corresponded with a 50% reduction in the slope of the left ventricular function curve, a reduction previously noted to be compatible with prolongation of life by the institution of IABC.⁹ This value compares well with the range of .5-.75 in which IABC was found by Phillips, to be beneficial and the value of .7 above which uniform sub-endocardial coronary perfusion was noted by Buckberg.¹

The demonstrated relationship between EVR and myocardial contractility implies that future therapy in patients with prolonged hemorrhagic shock and myocardial failure should be directed toward improving coronary perfusion while relieving left ventricular afterload. IABC

has been shown to accomplish this in primary cardiogenic shock.^{2,3} The data obtained in this study coupled with our previous work⁹ support the potential of IABC as a useful modality in the treatment of myocardial failure associated with hemorrhagic shock.

Although an $r = .72$ was obtained comparing the slope of the ventricular function curve with a simultaneously computed EVR, the variability of individual data points indicates that selection of patients for IABC therapy on the basis of their EVR would be hazardous.

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A Comparative Analysis of Warfarin and Low-dose Heparin as Thromboembolism Prophylaxis in Total Hip Replacement Patients

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Warfarin, low-dose heparin, or a combination of low-dose heparin and hydrocortisone was administered to 300 patients undergoing total hip replacement. The lowest incidence of thromboembolic (5 per cent) was attained with Warfarin. Further investigation into the method of administration of low-dose heparin is necessary before it can be used effectively as thromboembolism prophylaxis in total hip replacement patients. The addition of hydrocortisone was not found useful.

PULMONARY embolism has been long recognized as a tragic complication of hospitalized patients. Most often this complication presents without clinical evidence of antecedent thrombophlebitis, and the episode is unheralded by clinical signs and symptoms.

The introduction of modern reliable techniques which detect the presence of almost all thromboses in the lower extremities, including the "silent" ones, has complemented the earlier necropsy work^{41,43,46} Using the ¹²⁵I-labeled fibrinogen test, authors have determined the incidence of deep vein thrombosis to be 24 per cent,³⁴ in their patients over 40 years old not prophylactically treated, 31 per cent,³⁸ 41 per cent,⁵⁰ 42 per cent,¹⁸ 44 per cent¹⁶ and 56 per cent²⁹ following major abdominal surgery. A higher incidence of thrombosis is generally reported in elderly patients, in patients with a history of thromboembolism, and in those patients undergoing extensive surgery.^{16,26}

¹²⁵I-labeled fibrinogen and venography techniques have been used to establish the incidence of deep venous thrombosis as greater than 45 per cent in patients who have undergone fixation of fractures of the proximal femur.^{7,14,19} However, clinically manifest thromboem-

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bolic complications in hip fracture surgery patients have been reported to be considerably less frequent, ranging in incidence from a low of 15 per cent⁴⁸ to a high of 39.3 per cent.⁴² Evarts and Feil¹³ performed venograms on 56 postoperative elective hip surgery patients and found 54 per cent to be positive for thrombosis.

Some papers have presented large groups of hip arthroplasty patients who received no thromboembolism prophylactic treatment, other than the usual conservative measures (Table 1 and 2). Many authors have expressed their dissatisfaction with the strictly clinical appraisal of deep vein thrombosis, noting that the frequency of thrombophlebitis found in a group of hospitalized patients is somewhat related to how vigorously this complication is sought. If we compare Table 1, hip arthroplasty series in which no patients received thromboembolism prophylaxis, with Table 2, controls in hip arthroplasty series where thromboembolism prophylactic medications were used, it is apparent that the series in Table 1 have a much lower incidence of reported thromboembolic complications than the series in Table 2. A possible explanation for this fact may be that the authors in Table 2 followed their control patients for evidence of thromboembolic complications much more carefully than those of Table 1, because they were interested in comparing their control patients with patients undergoing thromboembolic prophylaxis. Therefore, we consider the incidence of thrombophlebitis, as detected by clinical examination in untreated hip arthroplasty patients, is between 4

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TABLE 1. *Hip Arthroplasty Series in Which There Was No Thromboembolism Prophylaxis Employed.*

	Ring ³⁷ 1968	Johnston & Larson ²⁵ 1969	Patterson & Brown ⁵⁵ 1972	Evanski et al. ¹⁰ 1973	Langenskiöld & Paavilainen ²⁰ 1973	Maczynski et al. ³² 1973
Procedure	THR	THR	THR	THR	THR	THR
Total	128	543	368	102	116	216
% Phlebitis	2.3%	5.8%	6.0%	2.9%	0.9%	3.7%
% PE	0.8%	3.6%	1.4%	1.4%	0.0%	4.6%

and 34 per cent and the incidence of pulmonary embolism between 4 and 10 per cent.

Because deep venous thrombosis has been shown to be such a common and often serious postoperative complication of hip arthroplasty patients, the total hip replacement patients at the Indiana University Medical Center were subjected to several methods of aggressive thromboembolism prophylaxis. The relative incidence of thromboembolic disease with each form of prophylaxis was then studied.

Materials and Methods

Three hundred eighty consecutive total hip replacement arthroplasties of the McKee-Farrar, Müller and Charnley design were carried out on 300 patients at the Indiana University Medical Center. The 80 patients who underwent bilateral replacements (26.7%) had both procedures performed concurrently. All operative procedures were either performed by, or strictly supervised by, a single physician (M.A.R.), who also directed their postoperative care. A nearly identical pre- and postoperative regimen was followed in each patient. The operative procedure varied little, with transposition of the greater trochanter and the use of two hemovac drains 24 to 48 hours postoperative in each case. The usual postoperative measures to prevent venous stasis in the lower extremities were employed. At the conclusion of each operation, both lower extremities were wrapped with compressive bandages from the toes to the hips, which were replaced by thigh length antiembolic stockings within a few days. During the first two postoperative days, the patients were placed at bed rest in a mild Trendelenburg position and function of their calf and thigh musculature encouraged. On the third postoperative day, the vast majority of patients were in acceptable medical condition to be sent to the Physical Therapy Department for tilt-

table standing, progressing to ambulation with a walker or crutches as quickly as possible. As may be expected, the patients who underwent bilateral replacement required more time for gait training in order to become functionally ambulatory. Their average duration of hospital stay was 21 days compared to 14 days for the unilateral replacement patients.

Four schemes of thromboembolism prophylaxis were used consecutively in this series. The Group I patient (108 cases) received 15 mg sodium Warfarin on the night of surgery. No Warfarin was given on the first postoperative day, but commencing on the second day, daily doses were given, based on the results of the daily prothrombin time test, with an effort to maintain the prothrombin time at twice the control value in seconds. The anticoagulant was continued throughout the duration of the hospitalization and tapered off over a two to three day period prior to discharge.

Group II patients (31 cases) received low-dose ("minidose") heparin as recommended by Kakkar et al.²⁷ and others.^{11,34} The Group II patients received 5,000 international units (IU) of sodium (lung) heparin subcutaneously two hours before surgery and then every 12 hours postoperatively, commencing 7 to 9 hours after surgery. The differences in this regimen from that of Kakkar was that these patients received their second dose of minidose heparin 7 to 9 hours postoperatively, instead of the 24 hours postoperatively, and they were maintained on it until discharge, instead of only 5 days. Because of excessive intraoperative and postoperative hemorrhage in this group of patients, it was not considered reasonable to continue the series after 31 patients.

Group III patients (71 cases) were treated identically to Group II patients with the exception that the minidose heparin was administered 8 hours, instead of 2 hours, preoperatively.

TABLE 2. *The Control Series in Which Thromboembolism Prophylaxis Was Studied in Hip Arthroplasty Patients.*

	Harris et al. ²⁰ 1967	Wilson et al. ⁵¹ 1972	Ruthermel et al. ³⁹ 1973	Coventry et al. ⁵ 1973	Lazansky ³¹
Procedure	CUP	THR	THR	THR	THR
Total	67	49	60	58	81
% Phlebitis	34.3%	14.3%	10.0%	3.4%	3.7%
% PE	10.4%	4.1%	6.7%	5.2%	6.2%

TABLE 3. The fractions represent the number of patients with that complication/number of patients in the group. The columns marked "P.E. and/or Phlebitis" represent the total number of patients in the group with thromboembolic complications and this number does not necessarily equal the arithmetic sum of patients in the "P.E." column and the "Phlebitis" column because some patients had both pulmonary embolism and phlebitis. Groups II, III and IV used low-dose heparin (LDH) alone or with hydrocortisone (HC).

	UNILATERAL			BILATERAL			ALL PATIENTS		
	P. E.	Phlebitis	P. E. &/or Phlebitis	P. E.	Phlebitis	P. E. &/or Phlebitis	P. E.	Phlebitis	P. E. &/or Phlebitis
GROUP I (Warfarin-108 pts)	0/78 (0%)	1/78 (1.3%)	1/78 (1.3%)	1/30 (3.3%)	3/30 (10.0%)	4/30 (13.3%)	1/108 (0.9%)	4/108 (3.7%)	5/108 (4.6%)
GROUP II (LDH 2 h preop-31 pts)	1/23 (4.3%)	3/23 (13.0%)	3/23 (13.0%)	1/8 (12.5%)	0/8 (0%)	1/8 (12.5%)	2/31 (6.5%)	3/31 (9.7%)	4/31 (12.9%)
GROUP III* (LDH 8 h preop-71 pts)	2/53 (3.8%)	4/53 (7.5%)	4/53 (7.5%)	2/18 (11.1%)	2/18 (11.1%)	3/18 (16.7%)	4/71 (5.6%)	6/71 (8.4%)	7/71 (9.9%)
GROUP IV (LDH 8 h preop-90 pts) + H. C.	0/66 (0%)	6/66 (9.1%)	6/66 (9.1%)	2/24 (8.3%)	2/24 (8.3%)	3/24 (12.5%)	2/90 (2.2%)	8/90 (8.9%)	9/90 (10.0%)

Group IV (90 cases) was identical to Group III except that in addition to minidose heparin, hydrocortisone phosphate 100 mg was administered intramuscularly three times daily one day preoperatively, on the day of operation, and on the first postoperative day.

These four groups were considered quite similar, and, therefore, comparable, as there was a nearly equal percentage of bilateral total hip replacement in each group, with the smallest percentage of bilateral cases in Group III (25%) and the largest in Group I (28%). Because of the known high incidence of thromboembolic complications in hip arthroplasty patients, it was not considered justifiable to include a control group of patients in this study who received no thromboembolic prophylaxis.

In evaluating these patients, thrombophlebitis was detected only by clinical means, and the classical signs of calf tenderness, warmth, edema, Homan's sign, and fever were sought. If a diagnosis of probable mild thrombophlebitis could be made with only one or two of the above signs present for several days, the case was considered a thromboembolic complication. Therefore, many of the cases of phlebitis reported here were quite mild. Also included in the study were cases of thrombophlebitis discovered in outpatients 3 to 6 weeks postoperatively. Pulmonary embolism was detected only after clinical symptoms and signs such as tachycardia, tachypnea, pleuritic chest pain, hemoptysis, and pleural friction rub became evident. All patients suspected to have sustained an embolism were subjected to routine laboratory investigation including electrocardiogram, chest roentgenogram, blood chemistry and enzyme determinations, arterial blood gas determinations, and lung scan to verify the diagnosis. In confirmed cases, appropriate treatment, usually consisting of anticoagulation with intravenous heparin, was promptly initiated.

An attempt was made to compare the amount of blood lost in the four groups of patients. The extensive laboratory work necessary to quantitate exactly the blood lost by each patient was not performed. Instead the total amount of blood transfused to each patient was tabulated. Although this method of estimating blood loss was

rather imprecise, most patients were transfused to a hematocrit of approximately 30 per cent, and the blood given to those patients who had extensive postoperative bleeding was included in the tabulation.

Results

A compilation of the thromboembolic complications in each group appears in Table 3. The lowest incidence of thromboembolic complications occurred in Group I with an incidence of 4.6 per cent, considering unilaterally and bilaterally operated patients together. The incidence of both thrombophlebitis and pulmonary embolism was lower in Group I than any other group. Although the overall incidence of thromboembolic complications was higher in Groups II, III and IV with rates of 12.0 per cent, 9.9 per cent, and 10 per cent respectively, only the patients in Group II had a higher than Group I incidence of thromboembolic phenomena that was statistically significant ($P < 0.05$) higher frequency of thrombophlebitis than the Group I patients.

In comparing bilaterally operated patients alone (only 80 patients), no significant difference was found in the incidence of phlebitis or embolism in the four groups.

The frequency of thromboembolic complications in the bilaterally operated patients was compared to the unilaterally operated patients in each group. The total incidence of thromboembolism was greater in the bilaterally operated patients in all groups except Group II. The incidence of phlebitis and total thromboembolic complications was significantly greater ($P < 0.05$) in the bilaterally operated patients of Group I only. The incidence of

TABLE 4. The Average Blood Replacement in Units (500 cc) Per Different Thromboembolic Prophylaxis.

	Unilateral	Bilateral
Group I (Warfarin)	2.5	5.7
Group II (LDH 2 h preop)	5.1	9.5
Group III (LDH 8 h preop)	3.0	6.7
Group IV (LDH 8 h preop) + H. C.	2.8	6.0

TABLE 5. *The Study Groups of Hip Arthroplasty Patients in Which Thromboembolism Prophylaxis was Employed.*

	Harris et al. ²⁰ 1967	Harris et al. ²¹ 1972	Harris et al. ²¹ 1972	Wilson et al. ⁵¹ 1973	Coventry et al. ⁵ 1973	Evarts et al. ¹² 1973	Johnston ²⁵ 1973	Lazansky ²¹ 1973	Rothermel ²⁹ 1973
Agent	Warfarin	Warfarin	Dextran	Warfarin	"Delayed"	Dextran	Dextran	Dextran	Dextran
No. Cases	70	114	113	51	1,950	200	256	104	60
Phlebitis	7%	2.6%	6.2%	0%	2.4%	7.5%	—	0%	6.7%
PE	0%	5.3%	6.2%	0%	1.1%	1.5%	2.3%	0%	5%

pulmonary emboli in the bilaterally operated patients was greater than twice that of the unilaterally operated patients in all groups. This was statistically significant in Group IV only ($P < 0.05$). Although statistical analysis does not confirm a higher incidence of thromboembolism in all groups, these data support the belief that bilateral surgery exposes the patient to an increased risk of thromboembolism.

The only fatal case of pulmonary embolism occurred in Group I. Two of the 4 cases of phlebitis in Group I were first noted at the routine 6-week postoperative visit. One of the 3 phlebitis cases in Group II was first noted 3 weeks postoperative, while 5 of the 8 phlebitis cases in Group IV were observed 3 to 6 weeks postoperatively. In Group III, all of the phlebitis cases were first diagnosed while the patients were hospitalized. Eight other patients in this study suffered severe arterial thromboembolic complications. In Group III, two patients suffered cerebrovascular accidents while two others developed arterial emboli in their lower extremities. In Group IV, there was one case of myocardial infarction, one cerebrovascular accident, and two lower extremity arterial emboli.

The average blood replacement in the four groups is shown in Table 4. The average quantity of blood given varied little between Groups I, III and IV. However, the average blood replaced in Group II patients was significantly greater than the patients of the other three groups. Excessive hematoma formation and wound bleeding, as well as intra-operative blood loss, was extremely common in this group. In Group II, 57 per cent of the unilaterally operated patients were transfused more than 4 units of whole blood, while 75 per cent of the bilateral cases received more than 8 units of blood, in sharp contrast to the other groups. Although the average amount of blood given to the Warfarin treated Group I patients was relatively small, these patients were noted to have a higher incidence of postoperative wound hematoma formation and larger hematomas than the Group III and IV patients. However, the rate of blood loss in hematoma formation was too gradual and the amount too small to result in an increase in the number of transfusions.

Discussion

Several clinical studies have demonstrated the efficacy of oral anticoagulants as thromboembolic prophylaxis in patients who have suffered hip fractures and other or-

thopaedic injuries^{19,41,42,48} and similar success with Warfarin has also been demonstrated.^{2,33} Fortunately there are several published series in which Warfarin has been used prophylactically in hip arthroplasty patients, and these series can be compared to our findings in Group I patients. Harris et al.²⁰ presented a controlled study of the use of Warfarin in mold arthroplasty patients. In their series, the treated patients had an incidence of thrombophlebitis of 7.1 per cent and of pulmonary embolism of 0 per cent compared to the control group in which the incidences were 34.3 per cent and 10.4 per cent respectively.

Low doses of heparin have been found to reduce dramatically the incidence of deep vein thrombosis, as detected by the ¹²⁵I-tagged fibrinogen technique, in postoperative patients.^{17,18,27,29,34,50} Several clinical trials have demonstrated the efficacy of minidose heparin⁴⁴⁻⁴⁷ and an excellent review of its use has recently been added to the literature.⁴⁹ Considering the evidence that many venous thrombi form during surgery,¹⁵ low-dose heparin has a theoretical advantage over conventional anticoagulation in that it has been given preoperatively without hemorrhagic complications. Therefore, we thought this agent could be useful in the prophylaxis of thromboembolism in total hip patients. Unfortunately, low-dose heparin, as it was administered in these patients, was not a remarkably effective method of thromboembolism prophylaxis. In our study, the incidence of thrombophlebitis in those patients receiving low-dose heparin (Groups II, III and IV) was approximately 9 per cent, an incidence above that in the other series of prophylactically treated hip arthroplasty patients reviewed (Table 5) and above that in two other series^{5,31} of untreated control patients (Table 2). The incidence of pulmonary embolism in Groups II and III of approximately 6 per cent is higher than that of all the other series of treated groups except that of Harris et al.²¹ and is not markedly less than that found in many of the untreated series. A lower incidence of embolism was noted in Group 5 (2%), but as explained previously, we hesitate to consider this figure significant, considering the approximately 9 per cent incidence of thrombophlebitis in this group. We must emphasize, however, that it is extremely difficult to compare meaningfully various series of patients because of their differences in patient management and because of the possibilities of observer bias. Two factors may contribute somewhat to a higher incidence of thromboembolism in this series. In

contrast perhaps to other series, an attempt was made to include quite mild cases of phlebitis. Secondly, this series contained a rather high percentage of bilateral operations compared to other series. Several small series of total hip replacement patients have been presented in which low-dose heparin has been used. The results in each series have been discouraging.^{4,11,28}

Past reports on low-dose heparin provide information that can be used to explain somewhat the poor results found in the use of that agent in total hip replacement patients. The mechanism of minidose heparin has been established by Yin and Wessler,⁵²⁻⁵⁴ who have shown that very low levels of heparin, much lower than that needed to block the thrombin-fibrinogen reaction, can greatly augment the anticoagulation effect of the naturally occurring activated factor X inhibitor. They believe that administration of low-dose heparin preoperatively can, by this newly discovered mechanism of action, prevent the development of the "hypercoagulable state" thought to develop early in the postoperative course. Since minidose heparin does not usually affect the whole blood clotting time, it has been used according to fixed schedules by all investigators except Sharnoff,⁴⁴⁻⁴⁷ who has used the Dale and Laidlow coagulometer to determine the dosage.

Recently, new sensitive assays have been developed, making it possible to measure extremely low heparin levels.^{1,9,28} Kakkar et al.²⁸ demonstrated a precipitous drop in the heparin level during surgery in patients who were injected 5,000 units of heparin subcutaneously two hours preoperatively, in sharp contrast to healthy non-operated subjects, who attained a more sustained level after the same injection. No good explanation is available concerning the phenomenon, but Kakkar thought that total hip patients had an increased requirement for heparin compared to other surgical patients and that perhaps higher and more frequent doses were necessary. Gallus et al.¹⁷ thought that three doses daily of 5,000 units of subcutaneous heparin was perhaps the reason for his lower rate of calf vein thrombosis in hip fracture and myocardial infarction patients compared to other series.

None of the low-dose heparin groups of the present study showed profound evidence of less thromboembolism compared to other series of total hip patients. Indeed the Group II patients demonstrated the hemorrhagic complications of administering 5,000 units two hours preoperatively. Studies using periodic heparin assays in low-dose heparin treated total hip patients would help determine the heparin dosage and interval preoperatively it should be given, as well as the most effective dosage and frequency postoperatively, without causing bleeding complications. It may well be advantageous to administer preoperative heparin between the 8 hours preoperatively of the Groups III and IV patients and the 2 hours preoperatively of the Group II patients. Low doses of heparin also may be more effective if started sooner

postoperatively than the postoperative interval of 7 to 9 hours used in the present study. Furthermore, giving heparin 3 or 4 times daily, rather than only 2 a day, may be helpful.

In our experience, Warfarin was apparently more effective than any of the minidose heparin regimes employed. However, the disadvantages of daily prothrombin times, use perioperatively and wound hematomas were encountered in the use of Warfarin. We hope that after further investigation, a better regime of minidose heparin administration may be established for total hip patients so that these relatively high risk patients may have the same low incidence of thrombosis found in other types of heparin treated surgical patients, without the need for daily laboratory work to avoid hemorrhagic complications.

Anti-inflammatory agents, most notably phenylbutazone, have been used successfully in the treatment of thrombophlebitis. The adrenal corticosteroids, long known for their anti-inflammatory properties, have been found to decrease thrombophlebitis as well as other symptoms in patients with certain rather rare autoimmune diseases.^{6,8,40} Hydrocortisone was, therefore, employed in addition to minidose heparin in the Group IV patients to determine the efficacy of glucocorticoids in the prophylaxis of thromboembolism. Steroids have been investigated concerning their possible effect on the blood fibrinolytic system. Although a decrease in the fibrinolytic activity of the blood of patients treated with corticosteroids has been observed,²³ contradictory work has demonstrated an increase in activity,³ leaving us no conclusion presently as to the effect of steroids on the fibrinolytic system.

A study of the Group IV patients of the present study appears to show that hydrocortisone was not efficacious in the prevention of thrombophlebitis. Perhaps the best explanation for this result is that, according to Hume, Sevitt and Thomas,²² the process of formation of deep venous thrombi is histologically noninflammatory. Therefore, anti-inflammatory agents are probably of little value in the prevention of venous thrombi, but are most likely useful only during the stage of organization and perivenous inflammation, long after the stage of thrombus formation. Further use of anti-inflammatory agents as thromboembolism prophylaxis is not recommended.

We therefore, do not recommend the use of low-dose heparin or hydrocortisone in the prophylactic treatment of thromboembolic disease associated with total hip arthroplasties.

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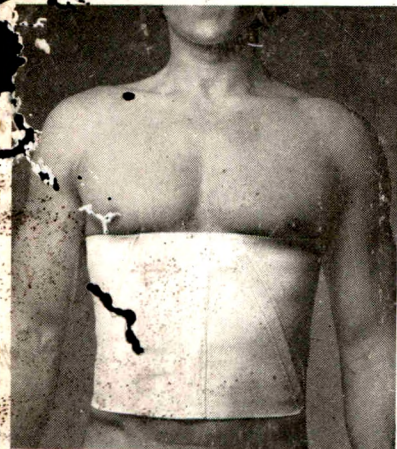
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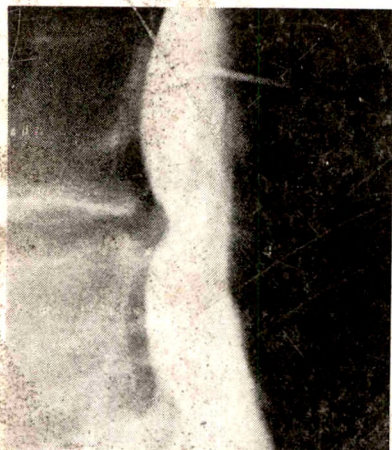
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